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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 Drs. Carome and Wolfe:

Thank you for contacting the Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS) and the Office of Research Oversight (ORO), Department of Veterans Affairs (VA) regarding your concerns about the study referenced above (letter dated August 1, 2017).

As you noted, the Myocardial Ischemia and Transfusion (MINT) Trial seeks to randomly assign 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 (RBC) transfusion strategy. The primary outcome measure of the trial is the composite of all-cause mortality (death from any cause) or recurrent nonfatal myocardial infarction within 30 days following randomization.

Eligible subjects are to be randomly assigned to either a restrictive RBC transfusion strategy or a liberal RBC transfusion strategy. Subjects assigned to the restrictive RBC transfusion strategy will be permitted to receive a transfusion if the hemoglobin concentration falls below 8 g/dL and will be strongly recommended to receive an RBC transfusion if the hemoglobin concentration falls below 7 g/dL. RBC transfusion also is permitted if angina symptoms (chest pain or discomfort, or chest pressure or heaviness) that are thought by the clinician to be related to anemia occur and are not controlled with anti-anginal medications. Packed RBCs (leukoreduced RBC units) will be administered one unit at a time, and enough RBCs will be given to increase the hemoglobin concentration above 7 – 8 g/dL or to relieve symptoms of uncontrolled angina.

Subjects assigned to the liberal transfusion strategy will receive one unit of packed RBCs following randomization and will receive enough packed RBCs to raise the hemoglobin concentration to at least 10 g/dL any time the hemoglobin concentration is detected to be below 10 g/dL. A post-transfusion hemoglobin measurement showing a hemoglobin level of at least 10 g/dL must be obtained.

A subject in either group may be given a transfusion of packed RBCs at any time without a hemoglobin level if the patient is actively bleeding and the physician believes an emergency transfusion is needed.

The primary aim of the study is to determine whether a liberal RBC transfusion strategy reduces the composite primary outcome in comparison with a restrictive RBC transfusion strategy. Secondary aims include determining whether a liberal RBC transfusion strategy reduces all-cause mortality within 30 days in comparison with a restrictive RBC transfusion strategy and whether a liberal RBC transfusion strategy reduces myocardial re-infarction within 30 days in comparison with a restrictive RBC transfusion strategy.

The MINT trial investigators' primary hypothesis is that among patients with an acute myocardial infarction and a hemoglobin concentration of less than 10 g/dL, the liberal RBC transfusion strategy will reduce the rate of the composite outcome of all-cause mortality or recurrent nonfatal acute myocardial infarction through 30 days after randomization in comparison to the restrictive RBC transfusion strategy.

Subsequent to receiving your letter, OHRP and ORO have had multiple discussions with personnel at the National Institutes of Health (NIH) with regard to the MINT trial, and both the protocol and the consent form have undergone a number of changes, as discussed below. We believe the changes significantly address concerns raised by Public Citizen with respect to the design of the study and the information disclosed to prospective subjects. Also, all IRBs reviewing this study have been given a copy of the Public Citizen letter prior to their review of the revised documents. In addition, we note a recent Canadian study (not reflected in the information discussed below), published in the New England Journal of Medicine on November 30, 2017,[1] that concluded that for patients

[1] Mazer CD, Whitlock RP, Fergusson DA et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med 2017;377:2133-44.

undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive strategy regarding red-cell transfusion was *not* inferior to a liberal strategy with respect to the composite outcome of death from any cause, myocardial infarction, or stroke, or new-onset renal failure with dialysis, with less blood transfused.

MINT Protocol Design:

1) You allege that the MINT trial protocol lacks the following:

   a. description of current usual-care RBC transfusion practices for patients who are hospitalized with acute myocardial infarction and anemia at those institutions that intend to enroll subjects in the MINT trial; and

   b. an accurate, complete, and clear summary of all of the available data from prior randomized clinical trials that compared a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease, which overall show a strong signal for a higher risk of death and myocardial infarction with a restrictive transfusion strategy.

Relevant sections of the Background portion of the protocol have been revised by the study team to read as follows:

> **"Systematic Reviews, Clinical Trials:** We have performed a systematic review of clinical trials evaluating transfusion triggers in a variety of populations that were published in the Cochrane database(32) and JAMA.(33) We have updated the review (34) and found that compared with higher hemoglobin transfusion thresholds (~10 g/dL), a hemoglobin transfusion threshold of 7 or 8 g/dL is associated with fewer red blood cell units transfused (mean difference, -1.22 units per patient), without adverse associations with mortality, cardiac morbidity, functional recovery, or length of hospital stay. The relative risk for the association of restrictive versus liberal transfusion on 30-day all-cause mortality was 0.99 (95% CI, 0.82 to 1.20).
>
> A recent meta-analysis of 11 selected trials enrolling patients with cardiovascular disease (including data obtained from authors from four trials) was recently reported. The risk ratio for the association between transfusion thresholds and 30-day mortality was 1.15 (95% confidence interval 0.88 to 1.50), but the risk of acute coronary syndrome in patients in the restrictive compared with liberal transfusion group was increased in nine trials (risk ratio 1.78, 95% confidence interval 1.18 to 2.70).(35). This analysis is limited by the fact that data are only included from 27% of the eligible trials. The results of a meta-analysis in cardiac surgery patients reports trend favoring liberal transfusion (36) but the results conflict with another analysis in cardiac surgery patients in which no trend was evident. (34)
>
> **Clinical Trials in Acute Coronary Syndrome**: Our systematic review identified two pilot clinical trials that included patients suffering an acute coronary syndrome. The first was a small

pilot trial including 45 patients with acute myocardial infarction.(37) Patients with hematocrit less than 30% were randomly allocated to a liberal (hematocrit <30%) versus restrictive (hematocrit < 24%) transfusion threshold. The primary clinical safety measurement of in-hospital death, recurrent myocardial infarction, or new or worsening congestive heart failure occurred in 8 patients in the liberal arm and 3 in the restrictive arm (p< 0.046). There were 2 deaths in restrictive group and 1 death in the liberal group. The authors concluded a definitive trial was urgently needed.

In contrast, the MINT pilot enrolled 110 patients and found the pre-defined primary outcome of death, myocardial infarction, or unscheduled revascularization within 30 days occurred in 6 patients (10.9%) in the liberal-transfusion strategy and 14 (25.5%) in the restrictive-transfusion strategy p=0.054). Death at 30 days was less frequent with liberal transfusion 1 (1.8%) compared to restrictive transfusion 7 (13.0%); p=0.032.

Overall, there were 2 deaths in the liberal transfusion strategy and 9 deaths in the restrictive transfusion strategy (relative risk= 3.74, 95% CI 0.80-17.49; p=0.09) when the two trials in acute coronary syndrome are combined.

Other Trials (38) with Signal of Harm from Restrictive Transfusion: The two most recently published trials also found a higher mortality in patients in the restrictive transfusion group in patients with ischemic heart disease. The Titre2 trial contrasted liberal transfusion (9 g/dL) and restrictive transfusion (7.5 g/dL) in postoperative patients undergoing cardiac surgery. The short-term outcomes were comparable between the transfusion strategies, but at 90 days follow-up, overall mortality was higher in the restrictive transfusion strategy than the liberal transfusion strategy (hazard ratio=1.64; 95% confidence interval, 1.00 to 2.67, p=0.045). In a cluster randomized trial in 939 patients with GI bleeding, the mortality was trending higher in subgroup of patients with underlying ischemic heart disease; liberal transfusion strategy was 3% and in the restrictive transfusion strategy was 12% (difference =10.7%; 95% confidence intervals -9.8 to 31.2; interaction p=0.11)

Variation in Transfusion and Guidelines: The systematic reviews of observational studies and randomized trials evaluating the impact of anemia and transfusion highlight the lack of any study with sufficient numbers of patients to guide clinical care. All of this uncertainty has helped fuel significant practice variation. Two older large studies in 44,242 patients with non-ST segment elevation myocardial infarction from 400 US hospitals(9) and 17,676 patients with acute myocardial infarction demonstrate substantial variation in transfusion.(10) Similar variation was observed in over 19,315 hospitalized patients with a discharge diagnosis of myocardial infarction during 2009-2012 from the California Kaiser Permanente Health System (Percent transfused at nadir hemoglobin level >10 g/dL, 0.2%; 9-9.9 g/dL, 12.5%; 8-8.9 g/dL, 48.9%; 7-7.9 g/dL, 78.3%; < 7 g/dL, 91.5%). (39) A significant proportion of patients had transfusion thresholds at every cut-off from 7 to 10 g/dL. An updated analysis demonstrates variation in hospital acquired anemia in 17,676 patients with myocardial infarction (40) and transfusion among 34,937 patients with a myocardial infarction hospitalized between 2000-

2008 in 57 centers. (41) In a retrospective cohort study based on the CathPCI Registry data from 2009 to 2013, the risk adjusted rates of transfusion by hospital varied from 0.3% to 9.3%. (42) The high transfusion hospitals used a threshold between 9 to 10 g/dL, and low transfusion hospitals used a threshold between 8 to 9 g/dL. More contemporary data in cardiac surgery patients from 2013 show continued variation in transfusion practice. (43)

The variation in transfusion practice may further be exacerbated by the great variability in the transfusion guideline recommendations. While all conclude that there are too few high-quality studies, recommendations vary widely among organizations. The American Red Cross, AABB, British Committee for Standards in Haematology were not able to recommend a course of action,(44, 45) the American College of Physicians recommends 7-8 g/dL in patients with heart disease but is silent in acute coronary syndrome patients;(46) the American College of Cardiology/American Heart Association suggests avoidance of transfusion unless hemoglobin less than 8 g/dL(47, 48); National Comprehensive Cancer Network recommends 10 g/dL threshold in patients with coronary heart disease including patients with acute coronary syndrome (49), National Blood Authority of Australia recommends 8 g/dL threshold (50), and the European Society of Cardiology recommends transfusion only in case of compromised hemodynamic status and hemoglobin less than 7 g/dL.(51) The recently published guidelines from the AABB concluded that there was insufficient evidence in patients with acute MI and did not provide a specific recommendation, (52) while the UK National Clinical Guidelines Centre recommended transfusion at 8 g/dL (53). Given the lack of high quality evidence to guide transfusion in patients with acute myocardial infarction, it is not surprising that there is variation in recommendations emanating from different organizations.

Despite the variation in guidelines for transfusion in patients with acute myocardial infarction, there has been a strong and consistent trend towards reducing the use of blood transfusion in the US. For example, red blood cell transfusions per 1000 US population fell by 13.9% between 2013 and 2015. (54) Data from California Kaiser Permanente Health System show that in 70,189 hospitalized patients with cardiovascular disease, the frequency of transfusion fell 25% between 2009 and 2013. (55) The pre-transfusion hemoglobin in patients with cardiovascular disease declined from 8.1 to 7.6 g/dL. This change in clinical practice may be due to the widespread implementation of blood management programs (54) and Choosing Wisely Campaigns which targeted "unnecessary" transfusions. (56)"

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.

In addition, to further protect subjects, a new inclusion criterion was added to the protocol. This new requirement is that "the patient's attending physician, with expertise in cardiovascular care, believes that both of the transfusion strategies are consistent with good medical care for the patient as determined by his/her clinical judgement." According to the protocol, the research team is required to contact the patient's physician to explicitly obtain confirmation that this is the case. The protocol was also amended to include an additional exclusion criterion to prevent patients from being enrolled in the trial "if the attending physician does not believe the patient is an appropriate candidate for the trial for any reason." In MINT, where the treatments assigned in the trial are tightly controlled versions of what clinicians may be doing as part of standard care, the trial treatments might not be incorporating all pieces of information that a clinician might otherwise have used in choosing the treatment for a particular patient. The new inclusion criterion will help ensure that patients for whom some aspect of their condition might make one or another arm an inferior choice for them, in the view of their clinician, will not be enrolled. Together, these new inclusion and exclusion criteria that have been incorporated into the protocol provide more protection to subjects than if a patient's attending physician was only required to affirm that equipoise existed.

MINT Study Consent

2) You allege that the MINT trial consent form lacks the following:

   a. "…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)). Specifically, the sample consent form states that "The purpose of this study is to determine at what blood count patients should be given a transfusion." This brief statement fails to convey the seriousness of the trial's actual primary purpose, which is to determine whether patients who have been hospitalized for a myocardial infarction are at greater risk of dying or suffering another acute myocardial infarction in the short term (30 days) if they are managed with a restrictive RBC transfusion strategy versus a liberal RBC transfusion strategy."

   b. "The same section of the consent form also states that "it is not known if patients [who are in the hospital with a heart attack and have low red blood cell counts and] who receive the blood transfusion do better or worse." This statement is at best incomplete and at worst misleading, given that the preponderance of the existing scientific evidence from prior randomized clinical trials comparing a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease overall shows a strong signal for a higher risk of death and myocardial infarction with a restrictive RBC transfusion strategy."

   c. "…reasonably foreseeable risks to the subjects (45 C.F.R. § 46.116(a) (2)): The consent fails to include the competing risks that may be associated with using a restrictive RBC

transfusion strategy (i.e., possible increased risk of death or recurrent myocardial infarction given the available evidence."

d. "…identification of any procedures that are experimental (45 C.F.R. § 116(a) (1)): A description of actual usual-care RBC transfusion practices for patients hospitalized with acute myocardial infarction and anemia that are currently being used at any particular institutions where subjects would be enrolled is needed to determine whether either of the RBC transfusion strategies being tested in the MINT trial should be described in the consent forms as experimental because they would alter the care that the subjects would otherwise receive if they were not enrolled in the trial."

As noted, a variety of changes were made to the consent form.

The consent form's discussion of the study purpose has been revised as follows:

"This study is to be done to find the best blood transfusion plan in patients with a heart attack. Healthy people in North America have red blood cell counts above 12. The red blood cell count measures the part of the blood that brings oxygen to the organs in your body. Patients who are in the hospital with a heart attack often have low red blood cell counts. Doctors can order blood transfusion to increase the red blood cell count but it is not known if patients who receive the blood transfusion do better or worse. There is no local standard of care for when to give the blood at our hospital and doctors use different red blood cell counts to guide their decision. Some decide to order a transfusion when the red blood cell count is below 10 and others wait until the count falls to 7 or 8 before ordering a transfusion. Doctors are unsure which plan is best. The purpose of this study is to determine at what red blood cell count patients should be given a transfusion in order to lower the risk of death, heart attacks and other health problems."

In addition, a comment in the sample consent form to the researchers notes that the sentences describing the local standard of care should be revised at each site to reflect whatever is the standard of care at that site. Furthermore, the principal investigator for the trial conducted a survey of the lead researchers at each of the sites, to elicit information about what type of treatment they would provide for certain types of patients, and what, if any, type of care was generally being provided at their site. The survey "document[ed] that there is great uncertainty about the best threshold for transfusion in patients with acute myocardial infarction as well as large variation regarding transfusion practice patterns among clinicians at all sites." Further, the survey established that "[t]he majority of hospital sites have transfusion guidelines, but almost all do not have guidelines specific to patients with acute myocardial infarction." The document provided by the principal investigator that includes the survey results and the investigators' interpretation is attached.

The consent form's discussion of the risks from participation has been revised 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, fluid 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:

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. Based 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.

Specifically, the revised protocol and template consent form now include more balanced and complete information regarding (a) scientific evidence from prior randomized clinical trials that compared a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease, and the purpose of the trial; (b) the reasonably foreseeable risks associated with the research; (c) usual-care RBC transfusion practices for patients who are hospitalized with acute myocardial infarction at the institutions that intend to enroll subjects in the trial; and (d) how the restrictive and liberal RBC transfusion strategies being tested under the MINT protocol may potentially affect the care of research subjects. In addition, the revised protocol includes a new inclusion criterion that the study team is required to confirm with the patient's attending physician, with expertise in cardiovascular care, that both of the transfusion strategies are consistent with good medical care for the patient as determined by the attending physician's clinical judgement. Further, the consent form has been revised to allow for the inclusion of site-specific information regarding local standard of care practices if such standardized practices are in place.

We appreciate your organization's continued commitment to the protection of human research subjects.

Please contact us if you have any questions or would like additional information.

Sincerely,

Lisa R. Buchanan, MAOM
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Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services

Doug Bannerman, Ph.D.
Executive Director
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Attachment: "RBC Transfusion Practice in Myocardial Infarction Patients MINT Site Operational Evaluation: Results and Interpretation August 29, 2017"

cc:
Dr. Carolyn Clancy, Executive in Charge, Office of the Under Secretary for Health, VA
Ms. Catherine Levy, National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)
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