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Doug Bannerman, Ph.D.
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**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 Drs. Menikoff and Bannerman:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) and the Department of Veterans Affairs' (VA's) Office of Research Oversight (ORO) immediately suspend enrollment in the MINT trial and launch a compliance oversight investigation of the research. The trial is funded by the NIH and may be conducted, in part, by employees of at least four VA medical centers (see enclosed letters of support). Based on our review of the protocol, sample consent form, and relevant background scientific literature, we are concerned that the trial, as proposed, fails 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 fails to satisfy the basic ethical principles upon which those regulations are founded.

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

The MINT trial, which was recently opened to enrollment, 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 (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 of randomization.

Our primary concerns about the MINT trial are as follows:

- (1) The MINT trial protocol lacks the following:
 - (a) 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.
- (2) As a result of the above deficiencies in the protocol, the institutional review boards (IRBs) that reviewed (or will review) the MINT trial did not (or will not) receive sufficient information to make key determinations required for approval of human subjects research under HHS regulations at 45 C.F.R. § 46.111(a) and to ensure that the research satisfies the Belmont Report's basic ethical principles of beneficence and respect for persons.² In particular, the IRBs lacked (or will lack) sufficient information to determine whether:
 - (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)); and
 - (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 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>. Accessed July 31, 2017.

(3) The sample consent form that apparently was reviewed and approved by the IRB at the Rutgers Robert Wood Johnson Medical School, the clinical coordinating center for the MINT trial, fails to provide an adequate description of the following basic elements of informed consent required by HHS regulations at 45 C.F.R. 46.116(a) and consistent with the Belmont Report's basic ethical principles of respect for persons:

(a) The purpose of the MINT trial (45 C.F.R. § 116(a)(1)): 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.

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.

(b) Reasonably foreseeable risks to the subjects (45 C.F.R. § 46.116(a)(2)): Although the consent form describes the usual risks of receiving RBC transfusions for anyone, it 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 noted in the preceding paragraph and discussed in detail below).

(c) The 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.

The following is a more detailed discussion of the design of and rationale for the MINT trial, including data from prior randomized clinical trials comparing a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease, as well as our concerns about serious regulatory and ethical lapses related to the trial and our requested actions.

I. Overview of the MINT trial's design³

The MINT trial is a randomized, unblinded, two-arm multicenter clinical trial. The researchers plan to enroll 3,500 patients age 18 or older who have the following:

- (1) either an ST-segment-elevation myocardial infarction or a non-ST-segment-elevation myocardial infarction that occurs on admission to the hospital or during hospitalization; and
- (2) a hemoglobin concentration less than 10 grams per deciliter (g/dL).

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 caused by inadequate oxygen supply to the heart) that are thought by the clinician to be related to anemia occur and are not controlled with anti-anginal medications. Packed RBCs (RBCs concentrated by removing plasma) 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 outcome for the trial is a composite of all-cause mortality and recurrent nonfatal myocardial infarction within 30 days after randomization. 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 infarction within 30 days in comparison with a restrictive RBC transfusion strategy.

³ Myocardial Ischemia and Transfusion (MINT) trial protocol, Version 6.0. December 28, 2016. https://www.citizen.org/system/files/case_documents/mint-trial-protocol.pdf. Accessed July 31, 2017.

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 with the restrictive RBC transfusion strategy.

II. The MINT trial protocol provides insufficient information for the IRBs to make the findings required for approval of research

HHS regulations for the protection of human subjects at 45 C.F.R. § 46.111(a) require that in order to approve research, the IRB must determine that the following requirements — which are grounded in the Belmont Report's basic ethical principles of beneficence and respect for persons — have been satisfied:

- (1) The risks to the subjects are minimized by using procedures that were consistent with sound research design and that do not unnecessarily expose subjects to risk (45 C.F.R. § 46.111(a)(1));
- (2) 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)); and
- (3) The information that is being provided to subjects when their consent is sought includes an adequate description of the trial's research procedures (including identifying which, if any, procedures are experimental) and reasonably foreseeable risks (45 C.F.R. §§ 46.111(a)(4) and 46.116(a)(1) and (2)).

However, our review of the MINT trial protocol reveals that information that is critical for IRBs to make the above determinations is lacking.

A. Failure to define current usual-care RBC transfusion practices

In order for an IRB to fully understand the MINT trial's reasonably foreseeable risks and make the above determinations, it must first have a robust understanding of what the current usual-care RBC transfusion practices are for patients who are hospitalized with acute myocardial infarction *at institutions that intend to enroll subjects in the trial*. However, the MINT trial protocol offers no such discussion of current usual clinical care. Instead, the protocol states the following:

- (1) "Guidelines provide conflicting advice. This has led to practice variation..."⁴

⁴ *Ibid.*

- (2) “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.”⁵

To support these general statements, the protocol cited two large, retrospective observational studies that assessed RBC transfusion patterns in patients who were hospitalized in the U.S. with acute myocardial infarction.^{6,7} However, neither study provides a sufficient basis for defining — even generally — current usual-care RBC transfusion practices in patients with acute myocardial infarction at the institutions intending to enroll subjects in the MINT trial or at any other institutions. The first study analyzed RBC transfusion data from patients hospitalized from 2004 to 2005,⁸ and the second examined data on patients hospitalized from 2000 to 2008.⁹ Thus, most of the data being used to describe what is usual care at the time the MINT trial was initiated were at least a decade old and may not reflect current RBC transfusion practices in 2017 at the institutions intending to enroll subjects. Moreover, neither study prospectively assessed the actual hematocrit or hemoglobin levels that were used as transfusion triggers by clinicians for specific clinical scenarios. Instead, both studies retrospectively analyzed large databases to group patients with acute myocardial infarctions based on their nadir hematocrit or hemoglobin levels and then reported the the proportion of patients in each group who received an RBC transfusion. These data do not allow the identification of specific hematocrit or hemoglobin triggers, along with clinical indicators, that were used to determine when RBC transfusion was initiated.

The MINT trial protocol also referenced a third study that retrospectively analyzed data on RBC transfusions in U.S. subjects compared with non-U.S. subjects who were enrolled in three large randomized clinical trials that tested different anti-thrombotic drugs for treatment of acute coronary syndrome.¹⁰ Subjects in the three trials were enrolled from 1994 to 1999,^{11,12,13} and the retrospective analyses of these trials provided no data on hematocrit or hemoglobin triggers that were used to determine when RBC transfusions were initiated.

⁵ *Ibid.*

⁶ Alexander KP, Chen AY, Wang TY, et al. Transfusion practice and outcomes in non–ST-segment elevation acute coronary syndromes. *Am Heart J.* 2008;155(6):1047-1053.

⁷ Salisbury AC, Amin AP, Reid KJ, et al. Hospital-acquired anemia and in-hospital mortality in patients with acute myocardial infarction. *Am Heart J.* 2011;162(2):300-309.e3.

⁸ Alexander KP, Chen AY, Wang TY, et al. Transfusion practice and outcomes in non–ST-segment elevation acute coronary syndromes. *Am Heart J.* 2008;155(6):1047-1053.

⁹ Salisbury AC, Amin AP, Reid KJ, et al. Hospital-acquired anemia and in-hospital mortality in patients with acute myocardial infarction. *Am Heart J.* 2011;162(2):300-309.e3.

¹⁰ Rao SV, Chiswell K, Sun JL, et al. International variation in the use of blood transfusion in patients with non-ST-segment elevation acute coronary syndromes. *Am J Cardiol.* 2008;101(1):25-29.

¹¹ The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med.* 1996;335(11):775–782.

¹² The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med.* 1998;339(7):436–443.

¹³ The PARAGON B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation.* 2002;105:316–321.

Thus, the protocol offers no basis for the IRBs to evaluate the assertion that “both transfusion strategies assessed in this trial” are indeed “widely used in clinical practice,” particularly at the institutions where subjects would be enrolled in the trial.

The IRBs responsible for reviewing the MINT trial must insist that the MINT trial investigators perform detailed surveys, prospective observational studies, or both to define current 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. These surveys and observational studies should identify the specific hematocrit or hemoglobin levels (or ranges of hematocrit or hemoglobin levels) that are used as triggers — along with any other clinical factors that are employed — to determine when packed RBCs are transfused in such patients. For those patients who reach the hematocrit or hemoglobin trigger levels for transfusion, these surveys and observational studies also should identify the levels of hematocrit or hemoglobin to which the patients usually are transfused or the number of packed RBC units that these patients usually receive. Without these data, it is impossible for the IRBs to determine the following:

- (1) How the MINT trial’s liberal and restrictive RBC transfusion strategies will affect the care of subjects relative to the usual clinical practice at the institutions intending to enroll subjects;
- (2) Whether either or both strategies should be considered experimental;
- (3) Whether the trial design should be modified to include a control group that actually represents usual clinical care and that would allow adequate real-time safety monitoring while the trial is ongoing in subjects who have potentially rapidly fatal disease; and
- (4) By extension, whether the risks to subjects are being minimized and are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result.

B. Failure to convey the strength of the signal for harm associated with a restrictive RBC transfusion strategy compared with a liberal strategy

In order for an IRB to make the determinations required under HHS regulations at 45 C.F.R. § 46.111(a) regarding the risks to subjects who would be enrolled in the MINT trial, it also must fully appreciate that the preponderance of the best scientific evidence available to date from prior randomized clinical trials strongly signals that a restrictive RBC transfusion strategy is less safe than a liberal strategy for patients with cardiovascular disease. However, although the MINT trial protocol makes reference to a “**Signal of Harm from Restrictive Transfusion**” in patients with cardiovascular disease, the presentation of background scientific literature in the MINT trial protocol fails to effectively convey the overall strength and consistency of this signal. This failure is especially troubling given the investigators’ hypothesis that the liberal RBC transfusion strategy will reduce the rate of the composite outcome of all-cause mortality or recurrent nonfatal acute myocardial infarction in comparison with the restrictive RBC transfusion strategy.

Highlights from key individual randomized clinical trials

The two largest randomized clinical trials to date that compared a restrictive with a liberal RBC transfusion strategy in patients with a history of or risk factors for cardiovascular disease both demonstrated a worrisome signal for harm with a restrictive strategy in this subgroup of patients:

- (1) The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS trial), which was published in 2011 and listed as a reference in the MINT trial protocol, enrolled 2,016 subjects undergoing hip replacement surgery who had either a history of or risk factors for cardiovascular disease.¹⁴ The FOCUS trial investigators found a trend toward a lower incidence of acute myocardial infarction among subjects assigned to a liberal RBC transfusion strategy (transfusion trigger: hemoglobin 10 g/dL) compared with those assigned to a restrictive transfusion strategy (transfusion trigger: hemoglobin less than 8 g/dL) (2.3% versus 3.8%; odds ratio, 0.60; 99% CI 0.30 to 1.19).

In addition, previously unpublished data from the FOCUS trial obtained from Dr. Jeffrey Carson, the lead FOCUS trial investigator¹⁵ — who is also the principal investigator for the MINT trial — showed that among the 1,267 subjects who had known cardiovascular disease, the incidence of acute coronary events was significantly lower with the liberal RBC transfusion trigger than with the restrictive transfusion trigger (2.7% versus 5.1%; risk ratio, 0.53; 95% CI 0.30 to 0.94).¹⁶

- (2) The Transfusion Indication Threshold Reduction (TITRe2) trial, which was published in 2015 and briefly discussed in the MINT trial protocol, enrolled 2,007 subjects undergoing cardiac surgery.¹⁷ The TITRe2 trial investigators found a higher mortality rate among subjects assigned to a restrictive RBC transfusion strategy (transfusion trigger: hemoglobin less than 7.5 g/dL) than among those assigned to a liberal transfusion strategy (transfusion trigger: hemoglobin less than 9 g/dL) (4.2% versus 2.6%; hazard ratio 1.64; 95% confidence interval 1.00 to 2.67; p=0.045).

Additional results strengthening the signal for harm with a restrictive transfusion strategy in comparison with a liberal RBC transfusion strategy were seen in the following two small randomized clinical trials that enrolled subjects with acute coronary syndrome — the same patient population being studied in the MINT trial:

¹⁴ Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med.* 2011;365:2453-2462.

¹⁵ Personal communication with Dr. Irene Cortés-Puch.

¹⁶ Cortés-Puch I, Wiley BM, Klein HG, et al. Restrictive red blood cell transfusion strategies in patients with cardiovascular disease: A meta-analysis. American Thoracic Society 2017 Conference. May 19-24, 2017. Washington, DC.

¹⁷ Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med.* 2015;372(11):997-1008.

- (1) The CRIT Randomized Pilot Study, which was published in 2011, enrolled 45 subjects who had an acute myocardial infarction and a hematocrit less than or equal to 30%.¹⁸ (Note that a hematocrit of 30% corresponds to a hemoglobin level of approximately 10 g/dL.) The subjects were randomly assigned to either a liberal RBC transfusion strategy (transfuse when hematocrit was less than 30% to maintain it at 30% to 33%) or a restrictive RBC transfusion strategy (transfuse when hematocrit is less than 24% to maintain it at 24% to 27%). Death at 30 days occurred in one subject (5%) in the liberal RBC transfusion strategy group and two subjects (8%) in the restrictive group. Even though this finding is in the same direction as most of the available mortality data from randomized clinical trials to date that compared a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease — favoring a liberal RBC transfusion strategy — we concede this trial alone is not informative because it was clearly under-powered to detect even trends in mortality or cardiovascular morbidity outcomes between the two trial groups.
- (2) The MINT pilot trial, which was published in 2013 and led by the principal investigator for the MINT trial, enrolled 110 subjects with acute coronary syndrome (87% of subjects) or stable angina (13% of subjects) who were undergoing cardiac catheterization and had a hemoglobin level of less than 10 g/dL.¹⁹ The subjects were randomly assigned to either a liberal RBC transfusion strategy (transfuse to maintain hemoglobin at 10 g/dL or greater) or a restrictive RBC transfusion strategy (transfusion permitted for symptoms of anemia or for hemoglobin less than 8 g/dL). The primary outcome of the trial — the composite of death, myocardial infarction, or unscheduled revascularization at 30 days after randomization — occurred in 14 subjects (25.5%) in the restrictive RBC transfusion strategy group and in six subjects (10.9%) in the liberal transfusion strategy group (risk difference = 15.0%; 95% confidence interval of difference 0.7% to 29.3%; $p=0.054$ and adjusted for age $p=0.076$). Particularly concerning was the finding of a statistically significant higher number of deaths at 30 days in the restrictive RBC transfusion strategy group than in the liberal group (13% vs 1.8%, $p=0.032$).

As explained in the MINT trial protocol, for these two prior trials combined, there were nine deaths among the subjects assigned to a restrictive RBC transfusion strategy and two deaths among those assigned to a liberal transfusion strategy (relative risk 3.74; 95% confidence interval 0.80 to 17.49; $p=0.09$).

Meta-Analyses

Consistent with the above findings from individual clinical trials are the results of two recently published meta-analyses:

¹⁸ Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). *Am J Cardiol*. 2011;108(8):1108-1111.

¹⁹ Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J*. 2013;165(6):964-971.e1.

- (1) One meta-analysis by Patel et al, which was not referenced in the MINT trial protocol, reported a trend toward a lower 30-day mortality with a liberal RBC transfusion strategy than with a restrictive RBC strategy in six randomized clinical trials that enrolled a combined 3,352 subjects undergoing cardiac surgery (odds ratio 0.70; 95% confidence interval 0.49 to 1.02; $p=0.06$).²⁰
- (2) A more recent meta-analysis by Docherty et al of 11 trials, which was discussed in the MINT trial protocol, compared the effect of a restrictive versus a liberal RBC transfusion strategy in 3,033 subjects with cardiovascular disease in a non-cardiac surgery setting.²¹ This meta-analysis found no statistically significant difference in 30-day mortality between the two subject groups, but pooled data from nine of the trials showed an increased incidence of acute coronary syndrome in subjects in the restrictive RBC transfusion arms in comparison with subjects in the liberal transfusion arms (risk ratio 1.78; 95% confidence interval 1.18 to 2.70; $p=0.01$; $I^2=0\%$).

A third meta-analysis by Cortés-Puch et al — which was presented at the American Thoracic Society 2017 Conference in May and has been submitted for publication²² — reinforces the prior research findings presented here that a restrictive RBC transfusion strategy is less safe than a liberal strategy for patients with cardiovascular disease.²³ For this meta-analysis, the authors expanded the data analyzed in earlier meta-analyses by requesting and obtaining from clinical trial investigators additional unpublished data on the incidence of mortality and myocardial infarctions.²⁴ Cortés-Puch et al included all published randomized clinical trials that compared restrictive with liberal RBC transfusion strategies and that included data on adult subjects with known cardiovascular disease. The endpoints of interest were the mortality rate and the incidence of acute coronary events (defined as myocardial infarction or unstable angina).

²⁰ Patel NN, Avlonitis VS, Jones HE, et al. Indications for red blood cell transfusion in cardiac surgery: A systematic review and meta-analysis. *Lancet Haematol*. 2015;2(12):e543-553.

²¹ Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *BMJ*. 2016;352:i1351.

²² Personal communication with Dr. Irene Cortés-Puch.

²³ Cortés-Puch I, Wiley BM, Klein HG, et al. Restrictive red blood cell transfusion strategies in patients with cardiovascular disease: A meta-analysis. American Thoracic Society 2017 Conference. May 19-24, 2017. Washington, DC.

²⁴ Personal communication with Dr. Irene Cortés-Puch.

Cortés-Puch et al identified 16 randomized clinical trials that met their inclusion criteria: five trials enrolled cardiac surgery patients;^{25,26,27,28,29} one enrolled patients with acute myocardial infarctions, of whom more than half underwent percutaneous coronary interventions (PCIs);³⁰ one enrolled patients undergoing PCI, most of whom had acute coronary syndrome;³¹ and nine included patients with known cardiovascular disease who were hospitalized for other reasons (elective vascular surgery,³² critical care,^{33,34} hip surgery or fracture,^{35,36,37} septic shock,³⁸ oncologic surgery,³⁹ and acute upper gastrointestinal bleeding⁴⁰).

The following are the key findings from the Cortés-Puch et al meta-analysis:

- (1) Mortality risk: All 16 trials reported data on the mortality endpoint. For the overwhelming majority of the trials — 13 of 16 — the point estimate for mortality risk favored the liberal RBC transfusion strategy over the restrictive strategy, with the risk ratio approaching statistical significance in two of these 13 trials. For the three trials in

²⁵ Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: Effect on patient outcome. *Transfusion*. 1999;39(10):1070-1077.

²⁶ Murphy GJ, Rizvi SIA, Battaglia F, et al. A pilot randomized controlled trial of the effect of transfusion threshold reduction on transfusion rates and morbidity after cardiac surgery. *Transfus Altern Transfus Med*. 2007;9 (Suppl. 1):41-42.

²⁷ Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. *JAMA*. 2010;304(14):1559-1567.

²⁸ Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. *Transfusion*. 2012;52(1):91-99.

²⁹ Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015;372(11):997-1008.

³⁰ Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). *Am J Cardiol*. 2011;108(8):1108-1111.

³¹ Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J*. 2013;165(6):964-971.e1.

³² Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am J Surg*. 1997;174(2):143-148.

³³ Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340(6):409-417.

³⁴ Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: A randomized pilot trial. *Crit Care Med*. 2013;41(10):2354-2363.

³⁵ Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*. 2011;365:2453-2462.

³⁶ Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. *Injury*. 2013;44(12):1916-1918.

³⁷ Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: The TRIFE randomized controlled trial. *Acta Orthop*. 2015;86(3):363-372.

³⁸ Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391.

³⁹ de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: A prospective, randomized controlled trial. *Anesthesiology*. 2015;122(1):29-38.

⁴⁰ Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet*. 2015;386(9989):137-144.

which the point estimate for mortality risk favored the restrictive RBC transfusion strategy, the risk ratio did not approach statistical significance.

For all trials combined, there were 163 deaths among the 2,770 subjects randomly assigned to the liberal RBC transfusion groups and 197 deaths among the 2,745 subjects randomly assigned to the restrictive transfusion groups. Overall, a liberal RBC transfusion strategy produced a trend toward a lower risk of mortality than did a restrictive transfusion strategy among all patients with known cardiovascular disease (relative risk 0.86; 95% confidence interval 0.72 to 1.03; $p=0.11$). There was no evidence of heterogeneity between the trials for the mortality endpoint ($I^2=0\%$).

- (2) Risk for acute coronary events: Nine of the included trials reported data on acute coronary events, and such events occurred in eight of the trials. For the overwhelming majority of these trials — seven of eight — the point estimate for acute coronary event risk favored the liberal RBC transfusion strategy over the restrictive strategy, with the risk ratio reaching statistical significance in one trial. For the one trial in which the point estimate for acute coronary event risk favored the restrictive RBC transfusion strategy, the risk ratio did not approach statistical significance.

For all trials combined, there were 28 acute coronary events among the 2,027 subjects randomly assigned to the liberal RBC transfusion groups and 52 such events among the 2,047 subjects randomly assigned to the restrictive transfusion groups. Importantly, a liberal RBC transfusion strategy was associated with a significantly lower risk of acute coronary events than was a restrictive strategy among all patients with known cardiovascular disease (relative risk 0.57; 95% confidence interval 0.36 to 0.88; $p=0.01$). There was no evidence of heterogeneity between the trials for the acute coronary events endpoint ($I^2=0\%$).

- (3) For the mortality and acute coronary event outcomes, the findings were consistent across three predefined subject subgroups: (a) subjects undergoing cardiac surgery; (b) subjects with acute coronary syndrome, undergoing PCI, or both; and (c) subjects hospitalized for other reasons. The findings also were consistent regardless of whether the restrictive hemoglobin threshold studied was less than 8 g/dL or was 8 g/dL or greater.⁴¹

In summary, the available data to date from all randomized trials that enrolled patients with documented cardiovascular disease strongly signal that a restrictive RBC transfusion strategy increases the risk of death and acute coronary events in comparison with a liberal strategy. The importance of these findings rests not in their definitive nature but rather the consistency of the finding overall in patients with cardiovascular disease. These findings raise serious doubt about whether there is true equipoise between the liberal and restrictive RBC transfusion strategies being tested in the MINT trial, as asserted in the protocol.

⁴¹ Personal communication with Dr. Irene Cortés-Puch.

To safeguard the rights and welfare of the subjects who would be enrolled in the MINT trial and to ensure that the trial is ethical and complies with HHS regulations for the protection of human subjects, it is imperative that the IRBs responsible for reviewing the trial be informed that the preponderance of the best scientific evidence available to date from prior randomized clinical trials strongly signals that a restrictive RBC transfusion strategy is less safe than a liberal strategy for patients with cardiovascular disease. This information undoubtedly is directly relevant to the IRBs' determinations as to whether the risks to subjects are being minimized and are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result. It also affects the IRBs' assessments regarding the information that should be communicated to prospective subjects when their consent is sought, which is discussed in greater detail below.

C. Reliance on flawed clinical practice RBC transfusion guidelines

In offering a rationale to justify the design of the MINT trial, the trial protocol presented a brief discussion of the existing published clinical practice transfusion guidelines, noting that “the guidelines provide conflicting advice.”⁴² Among the guidelines referenced in the protocol were the most recently published guidelines from the AABB (formerly called the American Association of Blood Banks)⁴³ and from the UK National Clinical Guidelines Center (NCGC).⁴⁴

The AABB recommends a restrictive RBC transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, and a restrictive RBC transfusion threshold of 8 g/dL for hospitalized adult patients who are undergoing orthopedic surgery or cardiac surgery or have preexisting cardiovascular disease. The AABB refrains from making any recommendation about patients with acute coronary syndrome.

The UK NCGC recommends a restrictive RBC transfusion threshold of 7 g/dL for all adult patients, including those with known cardiovascular disease who do not have major hemorrhage or acute coronary syndrome. Disturbingly, the UK NCGC endorses a restrictive RBC transfusion threshold of 8 g/dL for patients with acute coronary syndrome.

Thus, both the AABB and UK NCGC transfusion guidelines affirm that a restrictive RBC transfusion trigger, in general, is as safe as a more liberal strategy for hospitalized patients, including those who have existing cardiovascular disease. Although this appears to be true for hospitalized adult patients without cardiovascular disease or the other aforementioned extenuating factors, the preponderance of the available evidence from randomized clinical trials, as discussed in detail above, strongly suggests that this is not true for hospitalized patients with existing cardiovascular disease.

⁴² Myocardial Ischemia and Transfusion (MINT) trial protocol, Version 6.0. December 28, 2016.

https://www.citizen.org/system/files/case_documents/mint-trial-protocol.pdf. Accessed July 31, 2017.

⁴³ Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. *JAMA*. 2016;316(19):2025-2035.

⁴⁴ Alexander J, Cifu AS. Transfusion of red blood cells. *JAMA*. 2016;316(19):2038-2039.

Importantly, the overall results from trials that assessed different RBC transfusion triggers indicate that a restrictive RBC transfusion strategy is safe in the general population of hospitalized patients and can save resources, but not lives.⁴⁵ In stark contrast, the preponderance of the best evidence available to date strongly signals that a restrictive RBC transfusion strategy is harmful in patients with cardiovascular disease and may cost lives. Moreover, it is highly plausible that among patients with cardiovascular disease, those with very serious disease who are experiencing an acute myocardial infarction or unstable angina are at greatest risk of harm from treatment with a restrictive RBC transfusion strategy: As the MINT trial investigators themselves acknowledge in their protocol, in the setting of acute coronary syndrome, myocardial ischemia may be worsened by low hemoglobin concentrations, especially in patients with coronary artery stenosis or active plaques.⁴⁶

It is unknown to what extent the AABB or UK NCGC transfusion guidelines are actually being followed by caregivers of patients with cardiovascular disease, particularly those who have acute myocardial infarction. The guidelines may be having little clinical impact because many clinicians likely follow the published scientific literature and are aware that the risk-benefit calculus derived from the existing evidence does not support the AABB or UK NCGC recommendations to use a restrictive RBC transfusion strategy for management of patients with cardiovascular disease.

Furthermore, both sets of guidelines were formulated on the incorrect premise that a liberal RBC transfusion strategy should be used only if it has been shown to improve patient outcomes compared with a restrictive strategy. For patients with cardiovascular disease — particularly those with acute coronary syndrome — a much more prudent approach would have been to formulate recommendations based on the premise that a restrictive RBC transfusion strategy should be adopted only when it has been shown to be as safe as a liberal RBC transfusion strategy.

III. Inadequate informed consent

Consistent with the Belmont Report's basic ethical principles of respect for persons, HHS regulations for the protection of human subjects at 45 C.F.R. § 46.116(a) require that when seeking the consent of prospective subjects for research, investigators provide, among other things, the following information:

- (1) An explanation of the purposes of the research, a description of the procedures to be followed, and identification of any procedures that are experimental (45 C.F.R. § 116(a)(1)); and

⁴⁵ Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art.No.: CD002042.

⁴⁶ Myocardial Ischemia and Transfusion (MINT) trial protocol, Version 6.0. December 28, 2016. https://www.citizen.org/system/files/case_documents/mint-trial-protocol.pdf. Accessed July 31, 2017.

- (2) A description of any reasonably foreseeable risks or discomforts to the subject (45 C.F.R. § 46.116(a)(2)).

However, the sample consent form⁴⁷ that apparently was reviewed and approved by the IRB at the Rutgers Robert Wood Johnson Medical School, the clinical coordinating center for the MINT trial, is seriously deficient with respect to these basic elements of informed consent.

A. Purpose of the research

As explained in the MINT trial protocol, the primary aim of the trial is to determine whether a liberal RBC transfusion strategy reduces the composite outcome of all-cause mortality or nonfatal myocardial infarction within 30 days after randomization compared 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 infarction within 30 days in comparison with a restrictive RBC transfusion strategy.

In contrast to the primary and secondary aims stated in the protocol, the sample consent form included the following explanation of why the study is being done:

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 blood 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, 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 blood count patients should be given a transfusion.

This explanation of the purpose of the MINT trial is deficient in several respects. First, the last sentence fails to convey the seriousness of the trial's true 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 as compared with a liberal RBC transfusion strategy. This same sentence also serves to obfuscate the serious outcomes of indelible harm being evaluated in the research.

Second, the statement that "There is no local standard of care for when to give the blood, and doctors use different red blood cell counts to guide their decision" may be true for hospitals

⁴⁷ Rutgers Robert Wood Johnson Medical School. Myocardial Ischemia and Transfusion (MINT) trial consent form. Version 6.2. January 23, 2017. https://www.citizen.org/system/files/case_documents/mint-trial-sample-consent-form.pdf. Accessed July 31, 2017.

affiliated with Rutgers Robert Wood Johnson Medical School, but it may not be true for all institutions intending to participate in this large, multicenter trial. Without data from detailed surveys or well-designed prospective observational studies of current 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, the IRBs have no basis for assessing the accuracy of the assertion that “there is no local standard of care for when to give the blood” in patients who have an acute myocardial infarction and anemia.

Third, the statement 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” 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 acute coronary events with a restrictive RBC transfusion strategy.

Importantly, in order to make a truly informed decision about whether to participate in the MINT trial, a reasonable person would want to know about the body of evidence from prior randomized clinical studies that consistently shows a strong overall signal that a restrictive RBC transfusion strategy is less safe than a liberal strategy for patients with cardiovascular disease. Of particular importance to a reasonable person would be the finding in the MINT pilot trial of a statistically significant higher number of deaths at 30 days in the restrictive RBC transfusion strategy group than in the liberal group.

B. Reasonably foreseeable risks

The MINT trial protocol provides the following statements regarding the risks of the research:

2.b Ethical Considerations

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** [emphasis added]. ...

2.e Risks and Benefits

In patients with heart disease, risks and benefits are considerably different than most other patient populations. Oxygen delivery to the myocardium is flow dependent since the heart extracts a high percentage of oxygen and myocardial ischemia may be precipitated or worsened by low hemoglobin concentrations, especially in patients with acute myocardial infarction. Anemia, if untreated may result in increased risks of further myocardial ischemia and injury. Transfusions, on the other hand, may result in increased risks of pulmonary edema and heart failure (Transfusion-Associated Circulatory Overload), from the significant amounts of volume given to patients with impaired ability of the heart to pump (systolic dysfunction) or ability to relax and fill (diastolic

dysfunction). Other adverse effects of allogeneic blood transfusion were also a concern: immunologic (transfusion-related acute lung injury... , and transfusion-related immune modulation... possibly leading to increased bacterial infections). Thus, there is clinical equipoise because it is unclear whether the benefits of immediate correction of anemia with transfusion are outweighed by the potential side effects of transfusion.

The sample consent form includes the following discussion of the trial's 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.

Like the explanation of the purpose of the trial, the consent form's description of reasonably foreseeable risks or discomforts to the subject is seriously deficient. Most significantly, the consent form, unlike the protocol, offers an asymmetric description of the trial's risks by only including the risks associated with transfusing packed RBCs to patients in general. Excluded from the consent form's description of risks is the possibility that subjects assigned to the restrictive RBC transfusion strategy group will die or suffer recurrent myocardial infarction because they did not receive an RBC transfusion that they might otherwise have received as part of usual clinical care if they had not enrolled in the trial.

Again, without data from detailed surveys or well-designed prospective observational studies of current 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, the IRBs are hamstrung in their ability to fully understand how the trial's liberal and restrictive RBC transfusion strategies will affect the care of and risks to subjects relative to the usual clinical practice at the institutions intending to enroll subjects.

In order to make a truly informed decision about whether to participate in the MINT trial, a reasonable person would want to know that some subjects participating in the trial may not receive an RBC transfusion when they otherwise would have if they had been receiving usual care, possibly resulting in increased risks of death and recurrent myocardial infarction. Likewise, a reasonable person would want to know that other subjects enrolled in the trial may receive an RBC transfusion when they otherwise would not, which may increase their risk of having complications related to RBC transfusion but also may decrease the risks of death and recurrent myocardial infarction.

C. Research procedures, including the identification of any procedures that are experimental

The sample consent form for the MINT trial does not identify any procedures as experimental. However, a description of current usual-care RBC transfusion practices for patients hospitalized with acute myocardial infarction and anemia that are currently being used at the 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.

IV. Conclusions and requested actions

The information presented in this letter raises serious, substantive concerns that the MINT trial, as designed and conducted, fails to materially comply with key requirements of the HHS and VA regulations for the protection of human subjects at 45 C.F.R. Part 46 and 38 C.F.R. § 16, respectively, and fails to satisfy the basic ethical principles upon which those regulations are founded.

Based on data from previously published clinical trials, the MINT trial investigators should have been aware that the preponderance of the available scientific evidence shows a strong signal that a restrictive RBC transfusion strategy is less safe than a liberal strategy and should have clearly communicated this evidence in their protocol to be reviewed by the IRBs. Regardless, in light of the additional data presented in the most recent meta-analysis by Cortés-Puch et al, it is imperative that the MINT trial be promptly reevaluated by the IRBs that previously approved the research.

We therefore urge the OHRP and ORO to immediately suspend enrollment in the MINT trial and require that the investigators take the following actions before considering whether the trial can resume:

- (1) Conduct detailed surveys, well-designed prospective observational studies, or both of current 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.
- (2) Revise the protocol to describe (a) the complete body of scientific evidence from prior randomized clinical trials that compared a restrictive with a liberal RBC transfusion strategy in patients with cardiovascular disease, which shows a strong signal for a higher risk of death and acute coronary events with a restrictive RBC transfusion strategy; (b) current 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 (c) how the restrictive and liberal RBC transfusion strategies being tested under the MINT protocol will affect the care of the subjects. Depending on the results of the detailed surveys and of observational studies of current usual-care RBC transfusion practices, the

trial may need to be redesigned to ensure that it is ethical (for example, inclusion of a usual-care control group may be warranted).

- (3) Revise the sample consent form so that it includes (a) an adequate explanation of the purposes of the research; (b) a description of the current evidence that shows a strong signal that a restrictive RBC transfusion strategy is less safe than a liberal strategy; (c) an adequate description of the reasonably foreseeable risks; and (d) identification of any procedures that are experimental.
- (4) Submit for review the revised protocol and sample consent form to the OHRP, ORO, and the IRBs responsible for reviewing the trial.

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

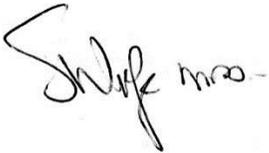
Thank you for your prompt attention to this important matter regarding the protection of human subjects. We look forward to the OHRP's and ORO's thorough and careful investigations into our concerns about serious regulatory and ethical lapses related to the MINT trial.

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
Public Citizen's Health Research Group

Enclosures

cc: The Honorable Thomas E. Price, Secretary of Health and Human Services
The Honorable Don Wright, Acting Assistant Secretary for Health, HHS
The Honorable Poonam L. Alaigh, Acting Under Secretary for Health, VA



DEPARTMENT OF VETERANS AFFAIRS
North Texas Health Care System

8 April 2016

Jeffrey L. Carson, MD
Study Chairman, MINT
Rutgers Robert Wood Johnson Medical School
125 Paterson Street
CAB Suite 2300
New Brunswick, New Jersey 08901

Dear Dr. Carson,

I am pleased to serve as the Site Principal Investigator at the VA North Texas Health Care System, for the Myocardial Ischemia and Transfusion (MINT) trial. I believe this study is poised to significantly impact the clinical care of patients with acute myocardial infarction since anemia is common and we are unsure of when to transfuse.

We have approximately 255 patients with myocardial infarctions per year, of which 5% are female patients

The racial breakdown of this population in 2015 was White-149, Hispanic- 14, African American- 70, Asian-2, American Indian- 4 and unknown-16.

Our research staff will actively recruit all eligible study subjects including those in the intensive/cardiac care and other units. We have a large research group of 9 coordinators and will be able to expeditiously complete start-up activities and recruit patients into the trial. I am confident that my colleagues in cardiology, internal medicine, and transfusion medicine will assist with the conduct of this high impact trial.

Sincerely,

A handwritten signature in black ink, appearing to read "Subhash".

Subhash Banerjee, MD; FACC; FSCAI
Professor of Medicine
University of Texas Southwestern Medical Center
Chief, Division of Cardiology
Co-director Cardiac Catheterization Laboratories
VA North Texas Health Care System, Dallas, TX
Phone: 214-857-1608
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Corporate Office: Dallas VA Medical Center, 4500 South Lancaster Road, Dallas, TX 75216
Sam Rayburn Memorial Veterans Center, 1201 East Ninth Street, Bonham, TX 75418
Fort Worth Outpatient Clinic, 2201 SE Loop 820, Fort Worth, TX 76119
Tyler VA Primary Care Clinic, 3414 Golden Road, Tyler, TX 75701



DEPARTMENT OF VETERANS AFFAIRS
Medical Center
1030 Jefferson Avenue
Memphis, TN 38104

In Reply Refer To:

April 5, 2016

Jeffrey L. Carson, MD
Study Chairman, MINT
Rutgers Robert Wood Johnson Medical School
125 Paterson Street
CAB Suite 2300
New Brunswick, New Jersey 08901

Dear Dr. Carson,

We have reviewed the number of patients admitted to our hospital with myocardial infarction and I look forward to working with you on this important trial. We commonly are faced with anemia in our MI patients and do not know if or when we should transfuse. These patients are typically very ill and we need high quality evidence to guide our blood management strategy.

We have approximately 100 myocardial infarctions per year, of which 2% was female. The racial breakdown is 58% Black/African American and 42% White. No other races were identified in my data review of the 2015 calendar year.

We are an experienced recruiting center for clinical trial and I am confident that we will be able to recruit from CCU, ICU and the medical floors of my medical center. I have 30 years of clinical trial experience. We were a highly successful site for the BARI 2D trial and are currently enrolling for the CIRT trial. We also are meeting our recruitment goals in the VA Coop PRESERVE trial and were successful in the VA Coop DIVA trial which recently ended the recruitment phase. I look forward to working with you on this practice changing study.

Sincerely,

Kodangudi B. Ramanathan, MD
Chief, Cardiology



Department of Internal Medicine

**CARDIOVASCULAR RESEARCH
GROUP OF ARKANSAS**



4300 West 7th Street, Slot 111-B

Little Rock, AR 72205-5484

501-257-5842

Investigator

April 12, 2016

Barry Uretsky, MD
Director
Principal Investigator

Abdul Hakeem, MD
Sub-Investigator

Zubair Ahmed, MD
Sub-Investigator

Jeffrey L. Carson, MD
Study Chairman, MINT
Rutgers Robert Wood Johnson Medical School
125 Paterson Street
CAB Suite 2300
New Brunswick, New Jersey 08901

Clinical

Dear Dr. Carson,

Kristin Miller, RN, CCRC
Clinical Research Coordinator

Kate Dishongh
Clinical Research Data Management

I am pleased to serve as the Site Principal Investigator at CAVHS for the Myocardial Ischemia and Transfusion (MINT) trial. I am routinely required to consider transfusion for complex patients with myocardial infarction. This important study will provide clinicians valuable evidence to inform that decision.

We have approximately 441 number of myocardial infarctions per year.. The gender and racial breakdown is:

Race	Female	Male	Grand Total
White/Caucasian	2	122	124
Black or African American	1	50	51
Unknown	0	8	8
Blank	5	252	257
Multi Racial	0	1	1

Department of Internal Medicine



**CARDIOVASCULAR RESEARCH
GROUP OF ARKANSAS**



4300 West 7th Street, Slot 111-B

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Our experienced research staff will actively recruit all eligible study subjects including those in the intensive/cardiac care and other units. Our coordinators/research nurse have over 12 years of experience. Recently, we have completed 2 MI trials. As the PI for our site, I have 30 + years of research experience. We have an established relationship of team work among the cardiologists, hospitalists, internists, and transfusion services and I am confident we can contribute to your important trial.

Sincerely,

A handwritten signature in black ink, appearing to read 'Barry Uretsky'.

Barry Uretsky, MD



DEPARTMENT OF VETERANS AFFAIRS
Jesse Brown VA Medical Center
820 South Damen Avenue
Chicago, IL 60612

30-Mar-2016
Jeffrey L. Carson, MD
Study Chairman, MINT
Rutgers Robert Wood Johnson Medical School
125 Paterson Street
CAB Suite 2300
New Brunswick, New Jersey 08901

Dear Dr. Carson,

I am pleased to serve as the Site Principal Investigator at Jesse Brown VA Medical Center (JBVAMC) for the Myocardial Ischemia and Transfusion (MINT) trial. I am routinely required to consider transfusion for complex patients with myocardial infarction. This important study will provide clinicians valuable evidence to inform that decision.

We have approximately 200 number of myocardial infarctions per year, of which 5% female. The racial breakdown is approximately 65% African American, 25% White, 5% Hispanic, 5% other races.

Our experienced research staff will actively recruit all eligible study subjects including those in the intensive/cardiac care and other units.

At our study site, at present we are enrolling study participants in 6 research protocols which are active in the Department of Cardiology at JBVAMC, 3 industry sponsored, one VA Cooperative study and 3 PI initiated protocols.

We have an established relationship of team work among the cardiologists, hospitalists, internists, and transfusion services and I am confident we can contribute to your important trial.

Sincerely,

A handwritten signature in black ink that reads "Mladen I. Vidovich".

Mladen I. Vidovich, MD, FACC, FSCAI

Chief, Section of Cardiology, Jesse Brown VA Medical Center
Associate Professor of Medicine, University of Illinois at Chicago
Governor for Department of Veterans Affairs, American College of Cardiology

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