October 26, 2016

Michael A. Carome, MD, Director
Sidney M. Wolfe, MD, Founder and Senior Advisor
Public Citizen Health Research Group
1600 20th Street, NW
Washington, DC 20009

RE: Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy . . .

Dear Drs. Carome and Wolfe:

This responds to your request of January 7, 2016, that the Department of Veterans Affairs (VA) Office of Research Oversight (ORO) conduct a compliance oversight investigation of the multisite research study described as "A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (PCI) (CHAMPION PHOENIX)" involving three Department of Veterans Affairs (VA) Medical Centers.

Public Citizen expressed the concern that the trial, as conducted at the VA facilities, "was unethical and failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. Part 16." Specifically, *Public Citizen* raised the concerns that:

(1) The CHAMPION PHOENIX research protocol failed to mandate appropriately timed antiplatelet therapy in control group subjects undergoing PCI, and that this omission resulted in the delay of appropriate antiplatelet therapy with Clopidogrel until after the subjects had undergone their PCI procedures, which represented substandard antiplatelet therapy that unnecessarily exposed subjects to risk. "Therefore, the design and conduct of the trial failed to ensure that risks to control group subjects were minimized, as required by VA human subjects protection regulations at 38 C.F.R. §16.111(a)(1)."

(2) When informed consent of the subjects was sought, the investigators failed to provide: "(a) an accurate description of the procedures to be followed for subjects randomized to the control group, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(1); (b) an adequate description of the reasonably foreseeable risks to subjects randomized to the control group, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(2); and (c) a complete disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(4)."

ORO conducted an onsite compliance investigation at the VA Boston Healthcare System (VABHS), located in Boston, Massachusetts on February 3-4, 2016, the VA North Texas Health Care System (VANTHCS), located in Dallas, Texas on February 17, 2016, and the Jesse Brown VA Medical Center (JBVAMC), located in Chicago, Illinois on February 24, 2016.

ORO evaluated the conduct of the CHAMPION PHOENIX trial by conducting interviews with the Principal Investigators, study staff, and the Institutional Review Board (IRB) Chairs, and by reviewing relevant

Institutional Review Board (IRB) and original primary source investigator records (inclusive of data collection tools, catherization laboratory reports, and medical records) for each enrolled and randomized study participant. ORO also conducted an independent evaluation of key study outcomes.

VABHS maintains its own IRB, and holds a Federalwide Assurance (FWA00001270) expiring February 16, 2017, with the Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP). VANTHCS has also historically maintained its own IRB, and holds a Federalwide Assurance (FWA00001338) expiring January 4, 2017. As of 2015, JBVAMC now maintains its own IRB, and holds a Federalwide Assurance (FWA00000290) expiring July 2, 2020. Prior to 2015, JBVAMC utilized the University of Illinois at Chicago (UIC) IRB as its IRB of record. The conduct of the CHAMPION PHOENIX study preceded the establishment of the JBVAMC IRB. The UIC IRB reviewed and approved the JBVAMC participation in the CHAMPION PHOENIX study.

FINDINGS

ORO established that the study and medical records associated with the randomized study subjects were complete and well organized, with details surrounding the PCI procedure and administration of study drugs comprehensively documented. The Principal Investigators (PIs) had clinical practices that included the conduct of a high volume of PCI procedures. Each PI routinely performed between 200 and 250 procedures annually, with junior study team members (co-investigators) each performing an average of 125 PCI cases per year.

A. Timing of Antiplatelet Therapy

The January 7, 2016, complaint precipitating ORO's review alleged that study subjects did not receive appropriately timed antiplatelet therapy. *Public Citizen* raised the concern that, "While the ideal timing for administration of Clopidogrel in the context of a PCI procedure had not been precisely defined, several pieces of evidence, multiple expert clinical practice guidelines, and other observations available to the investigators before the beginning of the trial established that delaying administration of Clopidogrel in patients undergoing PCI — particularly those presenting with STEMI or NSTE-ACS — until after the procedure constituted substandard antiplatelet therapy." Interviews with the study investigators found that the cardiac care teams at the three VA sites did not share the concern that administration of Clopidogrel after PCI constituted substandard antiplatelet therapy.

The three teams independently referenced multiple publications and emerging clinical practice guidelines concerning administration of antiplatelet therapy. However, none of the investigators agreed that administration of Clopidogrel after PCI constituted substandard antiplatelet therapy. To the contrary, each investigator referenced that the interdisciplinary nature of cardiac care at their facilities did not support the routine, standard of care use of Clopidogrel prior to PCI.

In accordance with standard of care clinical practice, patients and all participating subjects in the CHAMPION PHOENIX study were mildly sedated prior to undergoing coronary angiography. Following the angiogram, cardiac care teams convened and determined, depending on the disease state of the coronary vasculature, as to whether the patient was a candidate for PCI (balloon angioplasty and stent placement) or open heart surgery (CABG).

The investigators at VABHS, VANTHCS, and JBVAMC all described that CABG procedures occur in some 20-25% of cases. The investigators also stated that, given the elevated percentage of patients that did require CABG, surgical team concerns that patients preloaded with anticoagulants could experience bleeding-related complications during CABG informed institutional practices that did not routinely involve administration of Clopidogrel prior to the initial diagnostic coronary angiogram. Specifically, cardiac care teams did not routinely preload with Clopidogrel prior to the initial diagnostic angiogram because doing so introduced CABG

scheduling delays of up to five days associated with the patient clearance of Clopidogrel for patients who required surgery, and the attendant additional risk represented by the possibility of additional coronary events during the waiting period.

In addition, ORO's investigation revealed that the cardiac care protocols at the three VA facilities did not support routine administration of Clopidogrel after the coronary angiography and before the PCI. In particular, the cardiac care teams convened and determined the follow- up care (PCI or CABG) while the patient remained in the catherization laboratory suite. While the cardiac care team convened, the patients remained mildly sedated, in a supine position with the angiography wire in place, all of which contraindicated administration of oral medication. The investigators at the three sites all maintained that the possibility of side effects, when weighted against the long mechanism of action from ingestion, did not support routine administration of Clopidogrel pills before the PCI.

With respect to administration of Clopidogrel, participation in the CHAMPION PHOENIX study did not appear to result in a departure from the standard of care antiplatelet therapy for subjects enrolled at VABHS, VANTHCS, or JBVAMC. The investigation instead established that the lack of difference between the study and standard of care practices in the timing of Clopidogrel antiplatelet therapy did not result in any apparent additional research related risk for subjects assigned to the control arm. ORO's investigation therefore did not find evidence that either the investigators or IRBs were remiss in their responsibilities concerning minimization of study risk for subjects assigned to the control group.

B. Informed Consent

The January 7, 2016, complaint precipitating ORO's review also outlined concerns involving serious deficiencies in the informed consent process. *Public Citizen* raised the concern that, when informed consent of the subjects was sought, the investigators failed to provide, "an accurate description of the procedures to be followed for subjects randomized to the control group, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(1)." Of note, both the study team and subjects were blinded as to randomization assignment to either the Cangrelor group or the placebo infusion group.

In accordance with standard of care clinical practice, all participating subjects in the CHAMPION PHOENIX study provided documented clinical consent for the cardiac catheterization with PCI. The clinical informed consent document described the known risks and side effects of the clinically indicated treatment/procedure (PCI). Therefore, the IRBs had to ensure that the study informed consent document (ICD) clearly identified and described that the experimental aspect of the CHAMPION PHOENIX study involved comparison of the Cangrelor bolus and infusion to Clopidogrel standard of care therapy.

From interviews with the study team, and examination of the approved research ICDs at each site, ORO established that the sponsor's template language was used to describe the study procedures, including procedures to be followed for subjects randomized to the control group.

The sponsor's ICD template included the following description concerning the placebo group's study procedures: "Placebo Group – during the PCI procedure you will get placebo (a medically inactive substance) through an IV catheter inserted into your vein that will slowly inject into your body for at least 2 hours. However, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Per your institutions' standard of care, you will receive 2 – 4 150 mg capsules of Plavix at the time of the PCI. Finally, you will receive four (4) placebo capsules immediately after the placebo drip is stopped."

A review of individual subject records established that, consistent with the description in the ICD, the VA study

subjects completing the PCI procedure received 4 pills at the time of the PCI (over-encapsulated pink pill pack) and 4 pills post infusion (over-encapsulated blue pill pack).

ORO found that the ICD language "at the time of the PCI" lacked a degree of precision as to pill administration timing (i.e., the language would be equally accurate for pill administration before, during or immediately after the PCI). Additionally, ORO found that the study teams could have inserted the institutions' actual standard of care Clopidogrel dosing range described in the ICD, but instead retained the template language, "Per your institutions' standard of care, you will receive 2 – 4 150 mg capsules of Plavix at the time of the PCI."

Nevertheless, ORO found that the ICD and informed consent procedures used in the recruitment of prospective study subjects provided a reasonably accurate description of the procedures to be followed for subjects randomized to both study groups, including those assigned to the control group.

ORO also examined the *Public Citizen* concern that the ICD lacked an "adequate description of the reasonably foreseeable risks to subjects randomized to the control group." The expressed concern appeared predicated on the apparent understanding that study participants randomized to the CHAMPION PHOENIX control group would receive antiplatelet therapy inferior to standard of care, and that this "risk" was not acknowledged or described in the ICD. However, the review found that the actual pill administration procedures used as part of the study did not meaningfully alter, for any of the study subjects, the antiplatelet therapy (i.e., Clopidogrel dosing with respect to timing of administration or amount administered) they would have received as part of standard of care at the VA centers participating in the study.

As part of the investigation, ORO reviewed the adverse event information reported to the sponsor and other PCI-associated adverse events documented in the subjects' medical records. The analysis of available adverse event data associated with the VA study participants did not identify any significant study-related adverse risk that was omitted or insufficiently described in either the clinical or research ICDs.

Lastly, the review examined the *Public Citizen* concern that the ICD lacked "a complete disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects."

ORO found that the ICDs used by the VABHS, VANTHCS, and JBVAMC investigators all included a description of alternative courses of treatment. The VABHS ICD described other treatment available as follows: "Other treatment to that described above may include use of other medications and will be under the supervision of your doctor or caregiver. You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition." The JBVAMC ICD included language informing that, "You may choose to receive the standard treatments (including standard medications and diagnostic blood tests) for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition." The VANTHCS ICD included language informing that, "You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition."

Thus, ORO found that the ICDs used at VABHS, VANTHCS, and JBVAMC provided appropriate information concerning the availability of "standard treatments."

CONCLUSIONS

ORO did not substantiate the concern that the CHAMPION PHOENIX trial, as conducted at three participating VHA facilities, failed to satisfy the requirements of VA human subjects protection regulations. In particular, ORO did not substantiate the implicit concern that patients participating in the CHAMPION PHOENIX study

received antiplatelet therapy inferior to standard of care. ORO also did not substantiate the concern that the informed consent process was insufficient or otherwise inappropriate.

OFFICE OF RESEARCH OVERSIGHT

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John Thomas Puglisi, PhD
Executive Director

cc: Under Secretary for Health (10)
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