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International multicentre observational study to evaluate the association between perioperative red blood cell transfusions and 1-year mortality after major cancer surgery (ARCA-1): study design, statistical analysis plan and study protocol

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ABSTRACT

Introduction Blood transfusion is still common in patients undergoing major cancer surgery. Blood transfusion can be associated with poor prognosis in patients with cancer. Perioperative Care in the Cancer Patient -1 (ARCA-1) aims to assess in a large cohort of patients the current incidence, pattern of practice and associations between perioperative blood transfusions and 1-year survival in patients undergoing major cancer surgery.

Methods and analysis ARCA-1 is a prospective international multicentre observational study that will include adult patients scheduled to have major cancer surgical procedures with the intention to cure, and an overnight planned hospital admission. The study will be opened for 1 year for enrolment (7 January 2020–7 February 2021). Each centre will enrol patients for 30 days. The primary endpoint of this study is all-cause mortality 1 year after major cancer surgery. Secondary endpoints are rate of perioperative blood product use, cancer-specific mortality at 1 year and PFSs and 30-day morbidity and mortality.

Ethics and dissemination This study was approved by the Institutional Review Board at The University of Texas—MD Anderson Cancer Center. The study results will be published in peer-reviewed journals and disseminated at international conferences.

Trial registration number NCT04491409.

Strengths and limitations of this study

- This is an international prospective observational study that will report on transfusion practices worldwide.
- The study will be focused on short (ie, morbidity at 30 days) and medium-term outcomes (1-year mortality) after major cancer surgery.
- A limitation of the study is that there is no randomised intervention (blood transfusion). The lack of standardised transfusion practices (ie, triggers or ratios of blood products) is also a limitation of this study.
- Another limitation of the study is that oncological outcomes will be evaluated only 1 year after surgery. Therefore, late recurrences and mortality beyond 1 year will not be assessed in this study.

INTRODUCTION

In patients with cancer, the administration of packed red blood cells (PRBCs) or other blood products to treat severe or symptomatic anaemia or coagulopathies can be a life-saving medical intervention.[1] In the context of cancer surgery, PRBCs are often given perioperatively to treat acute and uncontrolled bleeding or anaemia. However, not unfrequently, PRBCs are also given perioperatively to patients without haemodynamic instability or symptomatic anaemia.[2] As a result, the rate of PRBCs transfusions during and after major cancer surgery remains variable, but it can be as high as 90% and in some cases, such as thoracic surgeries, several units (>10) of blood products are given perioperatively.[3–7]

Perioperative strategies of PRBCs transfusions may impact short-term clinical outcomes in patients with cancer. Several retrospective studies have demonstrated that transfused

patients have an increased risk of developing infectious and non-infectious postoperative complications after major cancer surgery.[8–10] However, the results from a recent randomised controlled trial (RCT) demonstrate that a restrictive approach in which transfusions were triggered by haemoglobin (Hb) lower than 7 g/dL increased the risk of postoperative complications when compared with a liberal approach (Hb <9 g/dL).[11]

Perioperative blood product transfusions may also impact long-term cancer outcomes (ie, recurrence and survival) by modulating the immune system, promoting inflammation and directly affecting cancer cells.[12] Amato and Pescatori[13] concluded in their meta-analysis that the odds of cancer recurrence were significantly increased in patients who received after preoperative, intraoperative and postoperative blood transfusions. However, that meta-analysis included data from RCTs and observational studies conducted more than two decades ago, which limits their generalisability mostly due to new advances in the treatment of colorectal cancers (ie, the increased popularity of robotic surgery and the associated reduction in blood transfusions).[13 14] Similar findings were reported in other meta-analyses.[3–5] However, a major problem of those studies were significant biases mainly due to their retrospective nature (not permitting, for instance, to separate the patients with symptomatic vs asymptomatic anaemia), which leads to not having accurate, timely prospectively collected information on patients as they undergo surgery and lack of statistical power.

Based on the limitations of the current studies in the literature, including in Amato and Pescatori study and recent evidence from observational studies suggesting that blood transfusions have a negative impact on cancer survival in other malignancies, we decided to design a large international multicentre observational study to evaluate the association between perioperative red blood cell transfusions and 1-year mortality after major cancer surgery across different solid malignancies .[13 15–20] The study is based on the hypothesis that perioperative PRBC transfusions in patients undergoing major cancer surgery are an independent risk factor of 1-year postoperative mortality. The study is also designed to investigate secondary outcomes, including rate and patterns of blood product transfusions and the association of different transfusion strategies with 30-day mortality and complications. We will also study the association between blood product use and 1-year progression-free survivals (PFSs).

MATERIAL AND METHODS

Study design

ARCA-1 is an international multicentre prospective observational study. The study is designed and will be conducted in accordance with the declaration of Helsinki. The study will be opened for 1 year for enrolment (7 January 2020–7 February 2021). The study is currently approved by the Institutional Board Review at the primary centre (#2020–0130), and it is registered online (www.clinicaltrials.gov).

Patient eligibility and enrolling strategy

Each participating centre will enrol during 1 month, and a minimum of 30 consecutive patients will undergo major surgery with the intention to achieve cancer cure. At the time of protocol development, 46 centres worldwide expressed their intention to participate in the study. Written informed consent will be obtained according to each centre Institutional Review Board or Ethic Committee local regulations.

Inclusion and exclusion criteria

Patients will be considered for inclusion in the study if they meet all the following criteria: (1) age ≥18 years, (2) American Society of Anesthesiologists physical status I–IV, (3) scheduled oncologic surgical procedures with the intention to cure and (4) an overnight planned hospital admission. Patients who: (1) have planned ambulatory, revision or palliative surgery, (2) undergo surgeries with minimum risk of blood transfusion (≤1%) during and after (48 hours) surgery according to each centre practice, (3) emergency procedures or (4) scheduled surgery under local infiltration anaesthesia are not eligible in the study. A decision to exclude surgeries with minimum risk of blood transfusion (≤1%) and those procedures done under local anaesthesia was made on the fact that the primary outcome of the study is all-cause mortality. Blood transfusions are not commonly given during and after low-risk surgical procedures (ie, simple thyroidectomies or breast lumpectomies).[21 22] Therefore, we speculate that the likelihood of blood transfusions impacting morbidity and mortality is low.

Exposure variable

Blood product transfusions are defined as the intravenous administration of PRBCs (any type), platelet concentrates, fresh-frozen plasma or cryoprecipitates preoperative (24 hours before surgery), intraoperative and postoperative (days 1 and 2 after surgery). Data on blood transfusions will be obtained from medical or blood bank records.

Primary, secondary and exploratory outcomes

The primary endpoint of this study is all-cause mortality 1 year after major cancer surgery. This endpoint hypothesis is that the perioperative (intraoperative or within 48 hours after surgery) transfusion of allogeneic RBCs is associated with a significant increase in risk in 1-year mortality. Secondary endpoints are the rate of perioperative blood product use, cancer-specific mortality at 1 year and PFSs and 30-day morbidity and mortality. We hypothesise that there are substantial geographic and cancer-related variations in the rate of perioperative blood product administration. Also, we hypothesise that allogeneic PRBCs transfusions are associated with significant increased morbidity and mortality 30 days after surgery, a significantly increased risk in cancer-specific mortality and shorter PFS. Exploratory outcomes include the rate of perioperative anaemia and the triggers of blood transfusions. The rates of perioperative coagulation disorders

and that of perioperative administration of fresh-frozen plasma, platelets and multi-component transfusion administration will be estimated.

Data collection and management

The study will be opened for patient enrolment for a period of 12 months, and each centre will choose 1 month for study entry. Site investigators at each participating centre will screen for patients according to inclusion and exclusion criteria. Investigators or study personnel will enrol consecutive patients presenting to surgery during the period of observation. All entered data will be de-identified to comply with data protection rights. Data will be collected intraoperatively, on day 0 (end of surgery until 11:59 pm), and postoperative days 1 and 2 from medical records. Each postoperative day is defined from 00:00 to 23:59. On day 30 postoperatively and 1 year from the day of surgery, follow-up data will be collected from each enroled patient. Follow-up data will also be collected from medical records.

Data collection will be performed using electronic case report forms in the Research Electronic Data Capture (REDCap, USA) via the internet. The Department of Anesthesiology and Perioperative Medicine at MD Anderson Cancer Center will create, maintain and grant access to the REDCap database. Site investigators will be granted access to the REDCap database after mandatory training. Each site investigator will enter the data directly into the REDCap database. Only a data analyst will have access to the database for the following tasks: monitoring, cleaning, audit trail creation, and exporting for statistical analysis.

Data quality and locking for analysis

During the patient enrolling period, data will be monitored weekly to detect aberrant patterns or anomalies, thus enhancing data quality. Site investigators will be contacted in case of missing and outlier data values as soon as these are detected. The database will be locked at the end of the study and as soon as missing or sources of errors in data are reviewed and corrected (whenever possible). At this step, the data will be reviewed before database locking. Then, the study database will be locked and exported for statistical analysis. According to The University of Texas—MD Anderson Cancer Center regulations, electronic files will be stored and secured under password protection.

Sample size and statistical analysis

ARCA-1 is an international observational study that plans to enrol a minimum of 2500 patients who undergo major cancer non-cardiac surgery. A full statistical analysis will be available before the end of inclusion. Table 1 provides the power calculations based on different scenarios when the total sample size is 2500, assuming a two-sided type I error rate of 0.05 (nQuery Advisor V.7.0). For example, when the total sample size is 2500 with a rate of perioperative PRBC transfusion of 10% (250 in the PRBC group and 2250 in the non-PRBC group), the study will have 84% power to detect the difference between the 1-year mortality rate of 10% for the PRBC group and 5% for the non-PRBC group (Scenario #2).

Demographical, intraoperative and postoperative variables will be collected (tables 2–5). Frequency counts and percentages will be reported for categorical variables (such as gender, race, the status of PRBC transfusion, morbidity at 30 days, mortality at 1 year, the status of preoperative anaemia and coagulation disorders). Summary statistics such as the number of non-missing observations (N), mean, median, SD and range will be provided for continuous variables (such as age, surgery time and length of hospital stay). The rate of 1 year mortality and its 95% CI for the The PRBC and the non-PRBC groups will be calculated. Fisher's exact test or χ^2 test will be used to evaluate the difference in the rate of 1-year mortality or cancer-specific mortality between the two groups. Overall survival (OS) and PFS rates at 1 year will be calculated. PFS will be estimated from the date of surgery to the date of progression or death whichever happened first. Kaplan-Meier method will be used to estimate the OS and PFS, and the log-rank test will be used to evaluate the difference in survival between the PRBC group and non-PRBC group. Multivariable Cox proportional hazards models may be used to evaluate the effect of PRBC on OS and PFS with the adjustment of other important covariates (ie, enrolling centre, malignancies and type of surgery), assuming that 250 events

Table 1 Sampe size calcultions

Scenario	Rate of perioperative blood transfusion	Sample size in the PRBC group (n_1) vs sample size in the non-PRBC group (n_2)	1-year mortality rate in the PRBC group (r_1) vs 1-year mortality rate in the non-PRBC group (r_2)	Power of the study to detect the difference in 1-year mortality rate (%)
1	0.10	250 vs 2250	0.10 vs 0.06	65
2			0.10 vs 0.05	84
3	0.15	375 vs 2125	0.10 vs 0.06	78
4			0.10 vs 0.05	93
5	0.20	500 vs 2000	0.10 vs 0.06	85
6			0.10 vs 0.05	96

n, sample size; PRBCs, packed red blood cells; r, rate.;

Table 2 Demographic and tumour variables

Demographics	Patients (n=)
Age (years)	Mean±SD
Sex (female/male)	n (%)/n (%)
BMI, kg/m^2	Mean±SD
ASA physical status	
1	n (%)
2	n (%)
3	n (%)
4	n (%)
Ethnicity	
Asian	n (%)
Black or African-American	n (%)
White	n (%)
Other	n (%)
Medical history	
Myocardial infarction	n (%)
Atrial fibrillation	n (%)
Coronary revascularisation	n (%)
Stent	n (%)
CABG	n (%)
Stroke	n (%)
Dementia	n (%)
Ongoing dialysis	n (%)
COPD	n (%)
Tobacco use	n (%)
Current	n (%)
Past	n (%)
Cancer history	
Primary/metastatic	n (%)/n (%)
Staging	
1	n (%)
2	n (%)
3	n (%)
4	n (%)
Neoadjuvant therapies	n (%)
CNS (brain/spine)	n (%)/n (%)
Head and neck	n (%)
Lung and bronchus	n (%)
Gastrointestinal	
Oesophageal	n (%)
Gastric	n (%)
Small intestine	n (%)
Colorectal	n (%)
Pancreatic	n (%)
Urological cancer	
Kidney	n (%)
Bladder/ureter	n (%)
Prostate	n (%)
Gynaecological cancer	
Cervix	n (%)
Ovarian	n (%)
Uterine	n (%)
Bone cancer	
Long bone	n (%)
Vertebral bone	n (%)
Pelvic bone	n (%)
Other	n (%)
Skin cancer	n (%)
Soft tissue sarcoma	n (%)
Peritoneal carcinomas	n (%)
Mesothelioma	n (%)
Blood transfusion history	n (%)
Preoperative autologous blood collection	n (%)
Preoperative anaemia management	
Iron therapy (p.o./intravenous)	n (%)/n (%)
EPO or similar	n (%)
RBC transfusion within 24 hours	
Irradiated	n (%)
Leucoreduced	n (%)
Number of units	Mean±SD
Age of oldest unit	Mean±SD
Preoperative coagulation management	
Platelet transfusion within 24 hours	n (%)
FFP transfusion within 24 hours	n (%)
Cryoprecipitate within 24 hours	n (%)
Anticoagulants within 24 hours	n (%)
Laboratory tests	
Haemoglobin (g/dL)	Mean±SD
Platelet count (×10^9/L)	Mean±SD
White blood cell count (×10^9/L)	Mean±SD
Prothrombin time	Mean±SD
INR	Mean±SD
aPTT	Mean±SD
Serum creatinine	Mean±SD
BNP	Mean±SD
NT-proBNP	Mean±SD
Troponin	Mean±SD
Thromboelastogram (TEG)	n (%)
Rotational TEG	n (%)
Platelet function assay	n (%)
Sonorheometry	n (%)

Continued

Table 2 Continued

Demographics	Patients (n=)
Blood type	
A	n (%)
B	n (%)
AB	n (%)
O	n (%)
Rhesus (Rh) factor (+/–)	n (%)/n (%)
Antibody presents	n (%)
Lewis	n (%)
MNS	n (%)
Xga	n (%)
Others	n (%)

aPTT, activated prothrobin time; ; ASA, American Society of Anesthesiologists; BMI, body mass index; BNP, Brain natriuretic peptide; CABG, coronary artery bypass graft; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; EPO, erythropoietin; FFP, fresh frozen plasma; INR, International normalised ratio; p.o, per os; RBC, red blood cells; TEG, thromboelastogram.

may permit to integrate up to 25 variables with an event per variable ratio of more than 10. The Kaplan-Meier product-limit method does not consider the competing nature of multiple causes to the same event (ie, death). Hence, Kaplan-Meier analysis may produce inaccurate estimates when analysing the marginal probability for cancer-specific events. Therefore, competing risk analysis will be considered to correctly estimate the marginal probability of an event in the presence of competing events. Given that this is a multisite cohort study with different providers and transfusion practices, we will consider using generalised estimating equations to handle unmeasured dependent between outcomes.[23] Subgroup analysis will be conducted for covariates known to influence our prespecified outcomes, including type of cancer, type of blood product (ie, allogeneic vs autologous, leukodepleted vs non-leukodepleted units), the timing of blood transfusions and number of units.

We realise that confounding bias between the PRBC group and non-PRBC group will inherently present in this non-randomised, observational study. Besides the analysis mentioned above, we will consider performing the propensity score matched (PSM) analysis to reduce the possible impact of the selection bias on the estimation of the difference in 1-year mortality rate between the two groups and to check the robustness of the results obtained with the multivariable Cox model. We will first decide on the set of potential confounding variables (ie, gender, cancer type and staging, type of anaesthesia technique used and surgical approach) to be used for the matching. We will then identify patient with PRBC and non-PRBC patients at a ratio of 1:1 (or 1:2 or 1:3 depending on the percentage of patients who received PRBC among

Table 3 Surgical and anaesthetic data

Operative report	Patients (n=)
Operation site	
Cranial intradural	n (%)
Spine	n (%)
Head (extradural) and neck	n (%)
Intrathoracic non-cardiac	n (%)
Intra-abdominal	n (%)
Intrapelvic	n (%)
Upper or lower extremity	n (%)
Cutaneous/superficial tissues	n (%)
Operation type	
Open	n (%)
Open-assisted laparoscopic	n (%)
Open-assisted robotic	n (%)
Robotic	n (%)
Multivisceral or multiorgan	n (%)
Anaesthesia report	
Anaesthesia duration (min)	
Dexamethasone use	n (%)
Anaesthesia technique	
General	
TIVA	n (%)
Volatile	n (%)
Combined	n (%)
Regional	n (%)
Neuraxial	n (%)
Spine	n (%)
Epidural	n (%)
Upper extremity	n (%)
Lower extremity	n (%)
Fascial plane	n (%)
Adjuv. anaesthetics/analgesics (intravenous/p.o.)	
NSAIDs	n= (%)
Gabapentinoids	Mean±SD
Acetaminophen	Mean±SD
Dexmedetomidine infusion	Mean±SD
Esmolol infusion	Mean±SD
Opioid analgesics (intravenous/p.o.)	
Fentanyl	Mean±SD
Morphine	Mean±SD
Hydromophone	Mean±SD
Tramadol	Mean±SD
Oxycodone	Mean±SD
Hydrocodone	Mean±SD
Mepedirine	Mean±SD
Intraoperative blood management	
Packed red blood cells	n (%)
Allogeneic	n (%)

Continued

Table 3 Continued

Operative report	Patients (n=)
Irradiated	n (%)
Leucoreduced	n (%)
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
Autologous	n (%)
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
Haemoglobin before transfusion	Mean±SD
Evidence of hypoperfusion	
Heart	n (%)
Kidney	n (%)
Bowel	n (%)
Extremity	n (%)
Brain	n (%)
Intraoperative platelet	
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
Intraoperative FFP	
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
Intraoperative cryoprecipitate	
Number of units	Mean±SD
Volume	Mean±SD
Intraoperative plasma concentrates	
Number of units	Mean±SD
Volume	Mean±SD
Intraoperative coagulation test	
Thromboelastogram (TEG)	n (%)
Rotational TEG	n (%)
Platelet function assay	n (%)

Adjuv, Adjuvant; FFP, fresh frozen plasma; NSAIDs, non-steroidal anti-inflammatory drugs; p.o, per os; TEG, thromboelastogram; TIVA, total intravenous anaesthesia.

all patients enrolled) using a 5 to 1 digit greedy match algorithm, and use absolute standardised differences to assess balance in the covariates between the PRBC case and non-PRBC groups. For scenario #2, when the sample size is 250 for the PRBC group, the sample size will be 750 for the non-PRBC group after PSM; if we identify PRBC patient and non-PRBC patients at a ratio of 1:3, the study will have 80% power to detect the difference between the 1-year mortality rate of 10% for the PRBC group and 5% for the non-PRBC group.

Table 4 Early postoperative data

Variable	Patients (n=)
ICU admission	n (%)
RBCs given POD-1 or POD-2	
Allogeneic	
Irradiated	n (%)
Leucoreduced	n (%)
Number of units	n (%)
Volume	Mean±SD
Age of oldest unit	Mean±SD
Autologous	n (%)
Number of units	n (%)
Volume	Mean±SD
Age of oldest unit	Mean±SD
Haemoglobin before transfusion	Mean±SD
Evidence of hypoperfusion	
Heart/hypotension	n (%)
Kidney	n (%)
Bowel	n (%)
Extremity	n (%)
Brain	n (%)
Platelets given POD-1 or POD-2	
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
FFP given POD-1 or POD-2	
Number of units	Mean±SD
Volume	Mean±SD
Age of oldest unit	Mean±SD
Cryoprecipitate given POD-1 or POD-2	
Number of units	Mean±SD
Volume	Mean±SD
Plasma concentrates given POD-1 or POD-2	
Number of units	Mean±SD
Volume	Mean±SD
Postoperative coagulation test before transfusion	
Platelet count	Mean±SD
PT	Mean±SD
aPTT	Mean±SD
INR	Mean±SD
Thromboelastogram (TEG)	n (%)
Rotational TEG	n (%)
Platelet function assay	n (%)
Medications given POD-1 and POD-2	
NSAIDs/Non-COX-2 inhibitor	n (%)
COX-2 inhibitor	n (%)
Opioids (any class)	n (%)
Acetylsalicilic acid	n (%)
Heparin or heparinoids	n (%)
Warfarin	n (%)

Continued

Table 4 Continued

Variable	Patients (n=)
Direct thrombin/Xa inhibitor	n (%)
ACEIs	n (%)
ARBs	n (%)
Direct renin inhibitor	n (%)
Loop diuretic	n (%)
Thiazide-like diuretic	n (%)
Potassium sparing diuretic	n (%)
Beta-blocker	n (%)
Alpha 2 agonists	n (%)
Aldosterone antagonist	n (%)
Hydralazine	n (%)
Insulin	n (%)
Oral diabetic drugs	n (%)
Postoperative complications	
Death	n (%)
Non-fatal cardiac arrest	n (%)
Myocardial injury	n (%)
Myocardial infarction	n (%)
Atrial fibrillation	n (%)
New or acute CHF	n (%)
DVT	n (%)
Pulmonary embolism	n (%)
Peripheral arterial thrombosis	n (%)
Amputation	n (%)
Pneumonia	n (%)
Stroke	n (%)
Delirium	n (%)
Acute kidney injury	n (%)
New dialysis	n (%)
TACO	n (%)
TRALI	n (%)
Infection attributed to transfusion	n (%)
Wound infection	n (%)
Sepsis	n (%)
Bleeding	
Requiring new operation	n (%)
BIMS	n (%)

ACEIs, angiotensin convertase inhibitors; aPTT, activated partial thromboplastin time; ARBs, angiotensin receptor blocker; BIMS, bleeding impacting mortality after non-cardiac surgery; CHF, congestive heart failure; COX-2, cyclooxygenase 2; DVT, deep venous thrombosis; FFP, fresh frozen plasma; ICU, intensive care unit; INR, International normalised ratio; NSAIDs, non-steroidal anti-inflammatory drugs; POD, postoperative day; PT, prothrombin time; RBCs, red blood cells; TACO, Transfusion acute cardiac overload; TEG, thromboelastogram; TRALI, transfusion-related acute lung injury.

Patient and public involvement

Patients or the public were not involved in the study design but will be involved in disseminating the results.

Table 5 One-year follow-up data

Variable	N(=)
Death	
Cancer-related	n (%)
Non-cancer related	n (%)
Cancer progression	n (%)
Non-fatal cardiac arrest	n (%)
Myocardial injury	n (%)
Myocardial infarction	n (%)
Atrial fibrillation	n (%)
New or acute CHF	n (%)
DVT	n (%)
Pulmonary embolism	n (%)
Peripheral arterial thrombosis	n (%)
Amputation	n (%)
Pneumonia	n (%)
Stroke	n (%)
Delirium	n (%)
Acute kidney injury	n (%)
New dialysis	n (%)
TACO	n (%)
TRALI	n (%)
Wound infection	n (%)
Sepsis	n (%)

CHF, congestive heart failure; DVT, deep venous thrombosis; TACO, transfusion acute cardiac overload; TRALI, transfusion-related acute lung injury.

ETHICS AND DISSEMINATION

All research activities regarding this study will be conducted according to national and international guidelines. According to each centre's Ethics Committee or Institutional Review Board guidelines, informed consent will be obtained by principal investigators or designated research personnel. In the case of waiver of consent, each centre will follow local guidelines.

The writing committee will draft the main manuscript and other reports generated by this research. The study Steering Committee will be in charge of manuscripts' approval and publishing the results of the study, whatever they are. We expect to have a main manuscript report findings from the primary and secondary endpoints. Other manuscripts may be published from substudies only after approval by the Steering Committee. All reports generated from this research will be submitted on behalf of the research group (ARCA and ASORG investigators). We plan to publish the list of collaborators in the online supplemental appendix. This list will include up to three investigators per enrolling site and published in alphabetical order according to the site's name.

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