

iNSPIRe

CliNical Science Program
for Independant Research



DOWNSTATE
HEALTH SCIENCES UNIVERSITY

Department of Surgery

Optimal Transfusion Strategy in High Cardiac Risk Patients after Major Surgery

Results of the TOP Trial



Roadmap

- From idea to application
 - Scientific justification, equipoise
 - Objective, eligibility, intervention, outcomes, measures
- Trial implementation
 - Recruitment
 - Randomized cohort, intervention adherence
- Results from the trial
 - Beyond p-values and reading between the lines
 - When the dust settles, nuance decides

Scientific justification

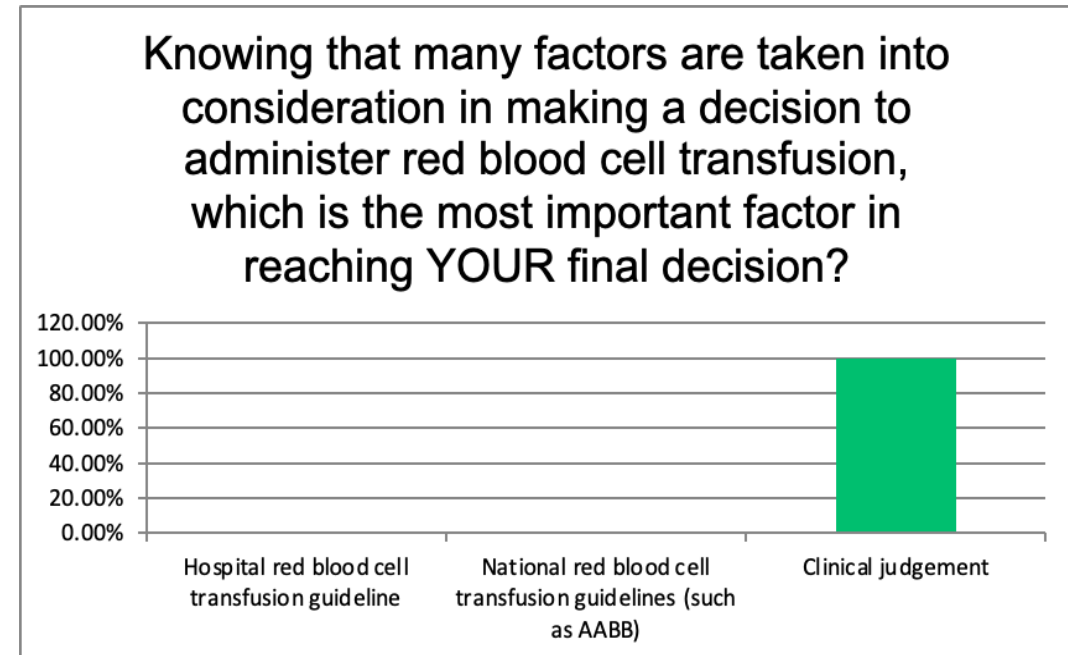
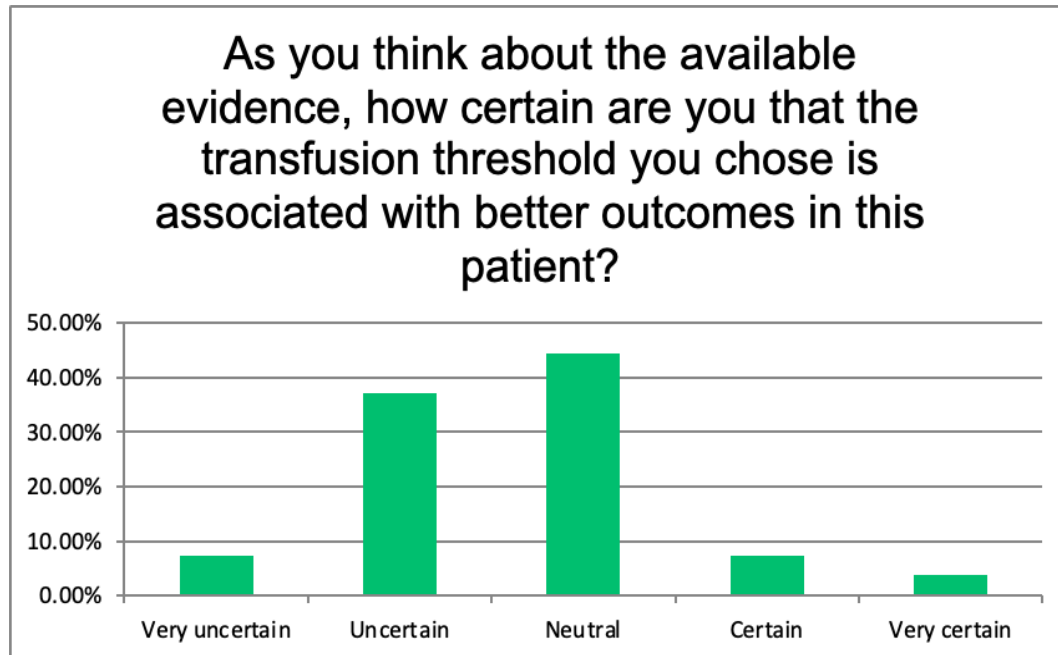
- Postoperative anemia is common after major operations.
- Current guidelines recommend transfusion for hemoglobin below 7 g/dL.
- Safety of this strategy is unclear, particularly...
 - After major operations, and
 - In high cardiac risk patients

Equipoise

- 70-year-old male patient POD 2 after aortobifemoral bypass graft
- Known stable coronary artery disease
- Small groin hematoma
- HR: 85, BP: 115/65 mmHg
- Hb: 9 g/dL (down from 13 g/dL preoperatively)
- **At what Hb level will you transfuse this patient?**

Equipoise

- Essential to reinforce engagement; trial fatigue is real



From justification to application

OBJECTIVE

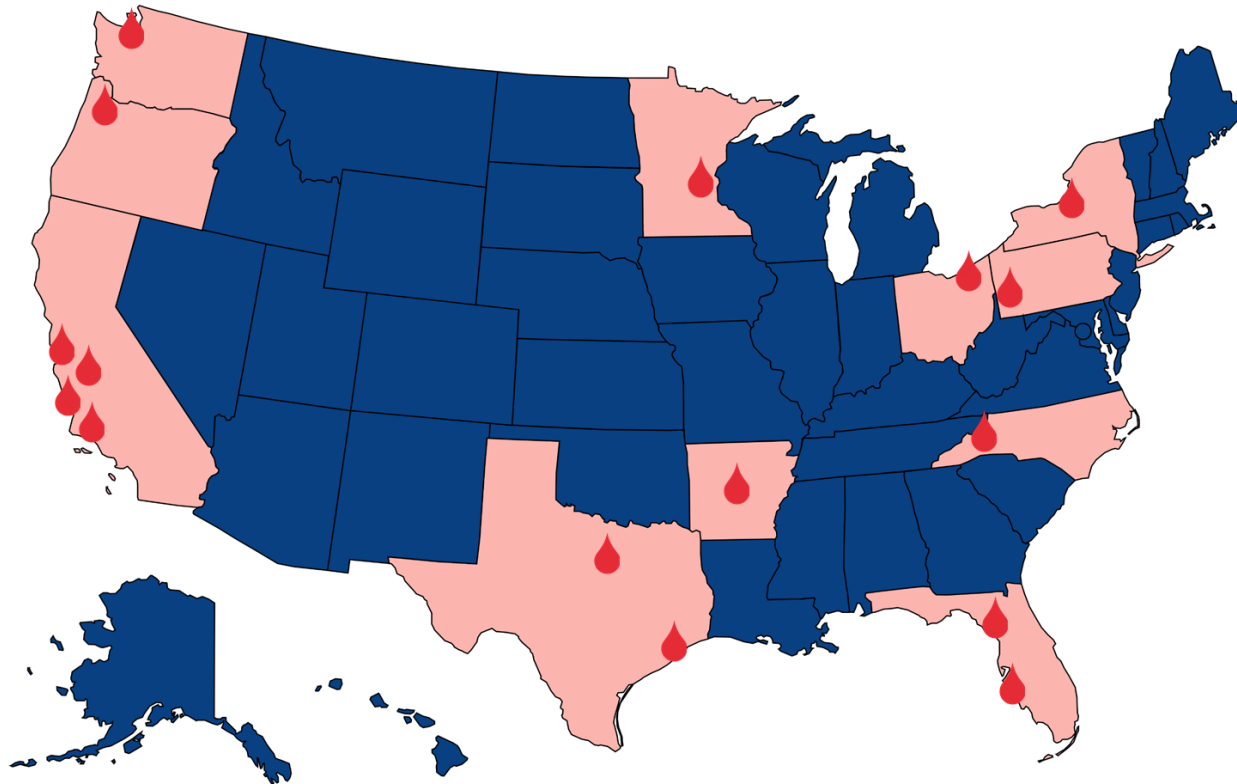
To evaluate whether in high cardiac risk patients undergoing major vascular and general surgery operations, a **liberal transfusion strategy** reduces the risk of **mortality or major ischemic events** compared to a **restrictive transfusion strategy**.

HYPOTHESIS

We hypothesized that following a **liberal strategy** the risk of adverse outcomes would be lower compared to a **restrictive strategy** in this high-risk postoperative cohort.

Study locations

Enrolled Veterans older than 18 years across 16 VA medical centers in this single-blinded, randomized controlled superiority trial.

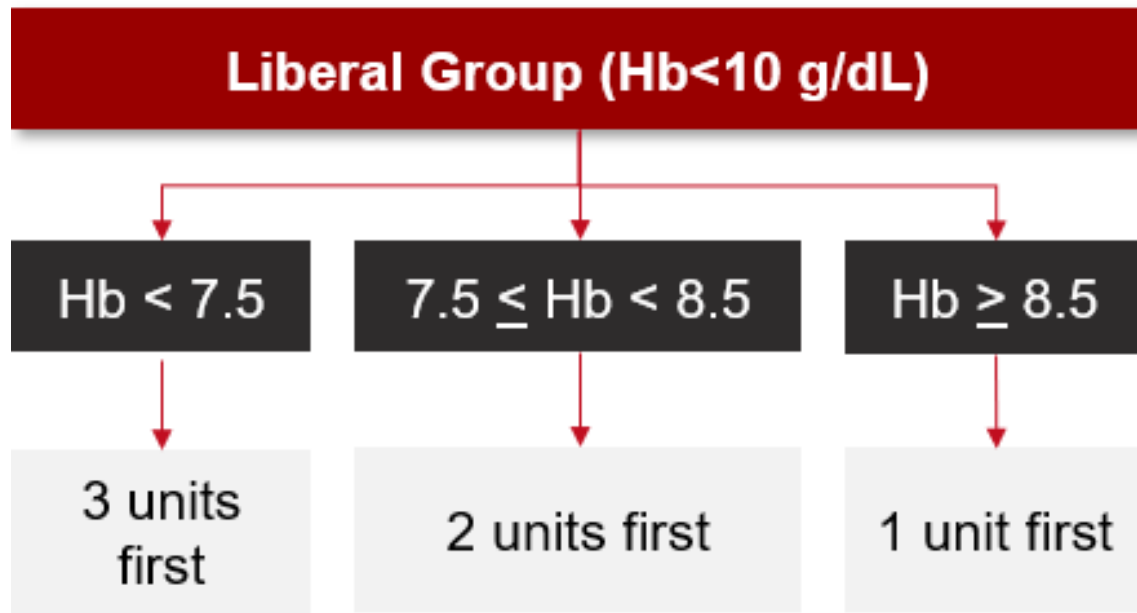


Asheville, NC
Buffalo, NY
Cleveland, OH
Dallas, TX
Gainesville, FL
Houston, TX
Little Rock, AR
Loma Linda, CA
Long Beach, CA
Minneapolis, MN
Palo Alto, CA
Pittsburgh, PA
Portland, OR
San Francisco, CA
Seattle, WA
Tampa, FL

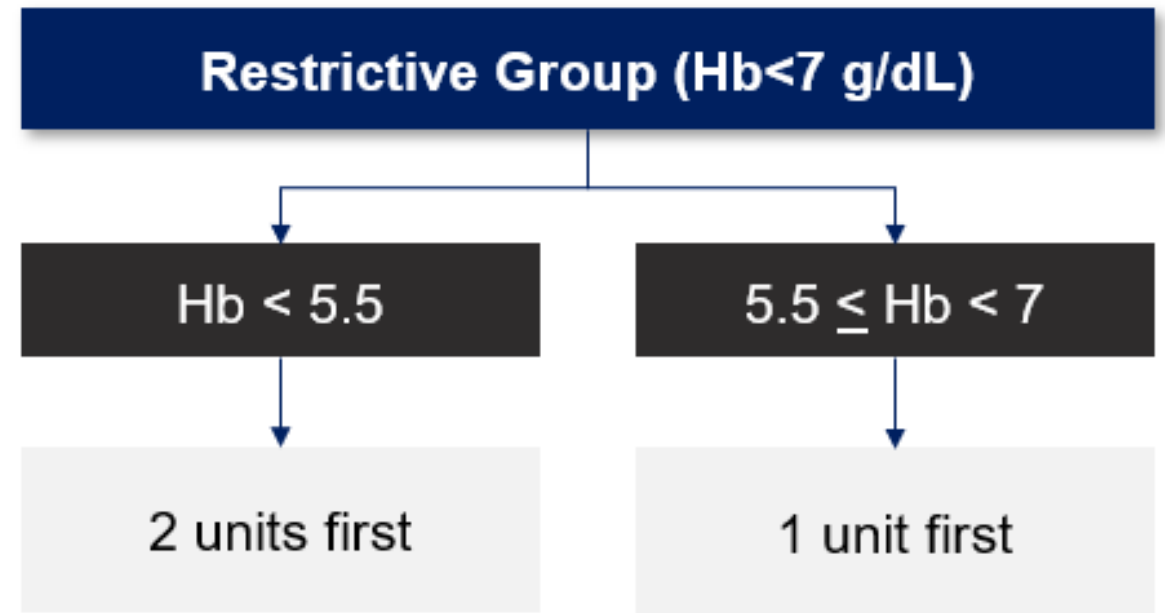
Eligibility

- Included patients who were undergoing a **major** general or vascular surgery operation and at high cardiac risk
 - **High cardiac risk:** History of ischemic heart disease, myocardial infarction, peripheral artery disease, stroke, or transient ischemic attack
- Excluded patients with history of hereditary anemia, bleeding disorders, previous adverse transfusion reactions, hemodynamic instability, or cardiogenic shock
- Randomized if postoperative anemia (Hb <10 g/dL) within 15 days of index eligible operation

Intervention | Transfusion strategies



Based on follow-up Hb, transfused to maintain **Hb ≥ 10 g/dL**



Based on follow-up Hb, transfused to maintain **Hb ≥ 7 g/dL**

Study outcomes



PRIMARY

Composite of:

- Mortality
- Myocardial infarction
- Coronary revascularization
- Acute renal failure
- Ischemic stroke

SECONDARY

Composite of non-MI cardiac complications

- New or worsening heart failure
- New cardiac arrhythmia
- Non-fatal cardiac arrest

SECONDARY

- Infectious complications at 90 days
- Length of stay
- Mortality at 1 year
- Primary outcome composite at 30 days

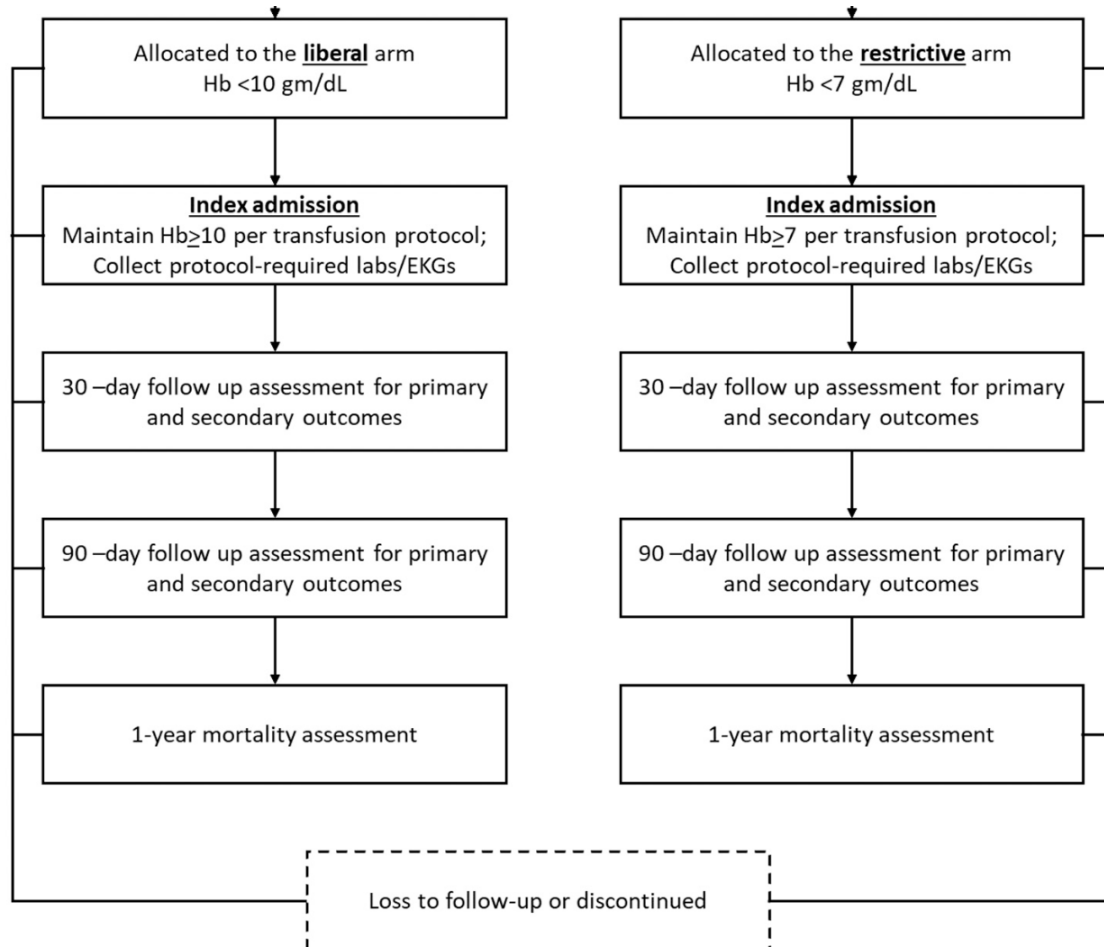
Within 90 days of randomization

Primary outcome definitions

- Mortality – all-cause
- Myocardial infarction – per the Third Universal Definition
- Coronary revascularization – percutaneous coronary stent or coronary artery bypass graft
- Acute renal failure – third stage or greater per RIFLE criteria
- Ischemic stroke – new unilateral neurological deficit for >24 hours and confirmed via imaging

All components of the primary outcome were adjudicated

Study measures

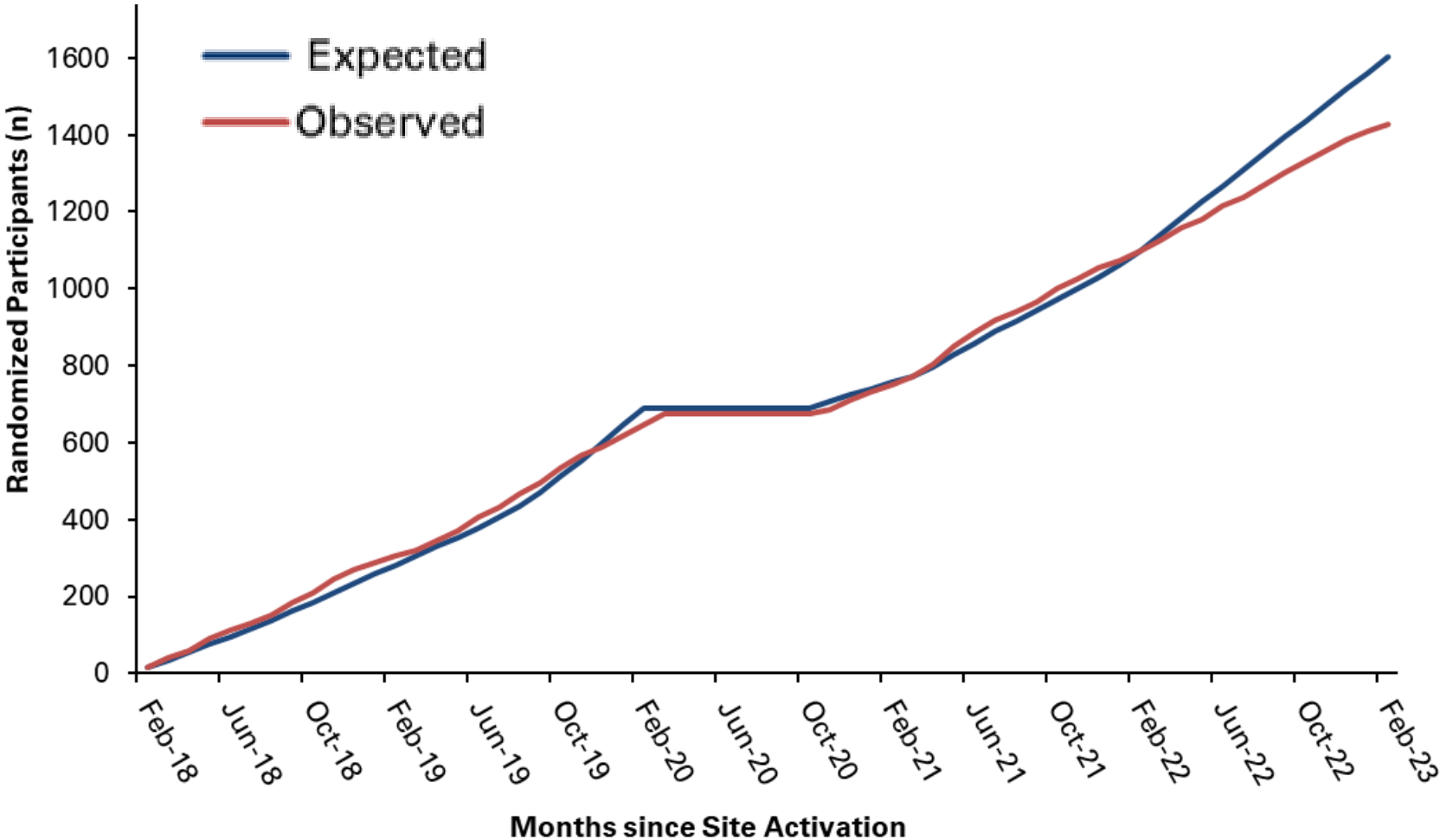


- In hospital labs and EKGs were collected for up to 7 and 4 days, respectively
- Follow up at 30- and 90-days for outcomes
 - Dual confirmation system
 - Visit compensation
- 90-day follow up complete for **96.1%**

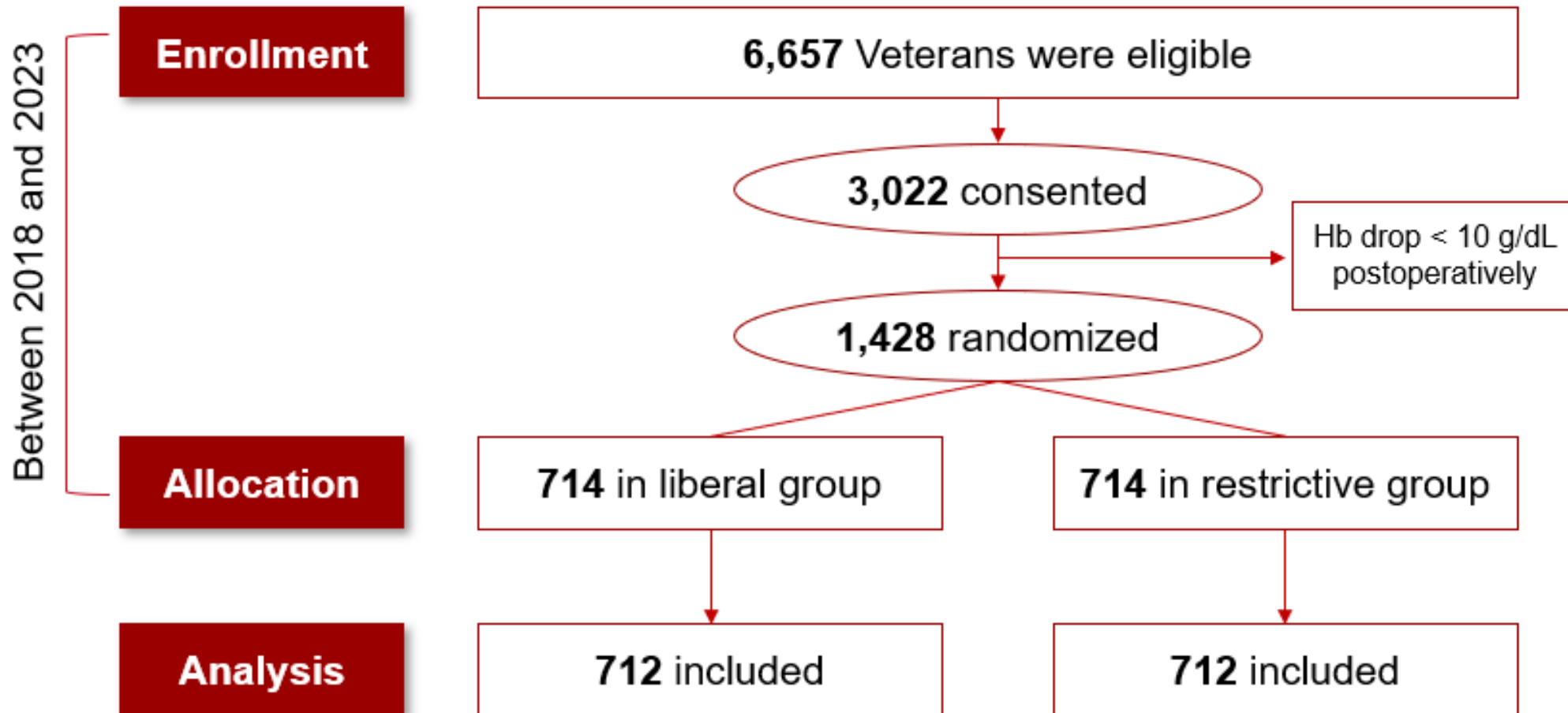
Sample size calculations

- Anticipated sample size was **1520 patients**
- Calculated to detect:
 - 25% relative difference at $\alpha=0.05$ with 90% power
 - 22.5% event rate in the liberal group
 - 30% event rate in the restrictive group
 - 5% attrition rate
- Intention-to-treat analysis

Recruitment



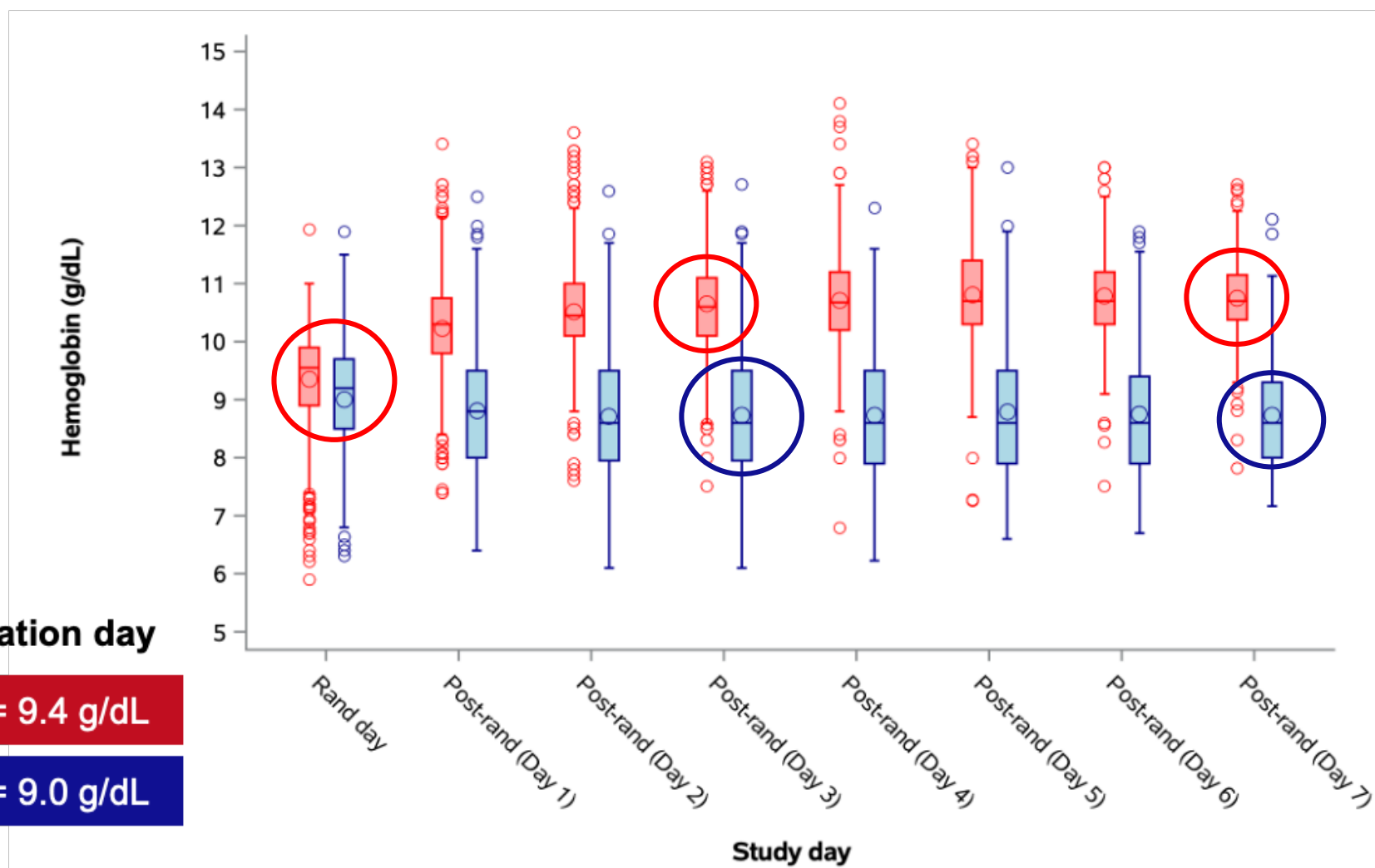
Randomized & analyzed cohort



Baseline characteristics

Characteristics	Liberal group (n=712)	Restrictive group (n=712)
Sex, n (%)		
Male	690 (96.9)	703 (98.7)
Female	22 (3.1)	9 (1.3)
Age, yr, <i>mean (SD)</i>	69.7 (8.2)	70.2 (7.7)
Race and ethnicity, n (%)		
Black or African American participants	143 (20.1)	125 (17.6)
White or Caucasian participants	523 (73.4)	548 (77.0)
Hispanic or Latino	25 (3.6)	33 (4.7)
Coronary artery disease, <i>n (%)</i>	416 (58.4)	428 (60.1)
Peripheral artery disease, <i>n (%)</i>	504 (70.8)	526 (73.9)
Vascular surgeries, <i>n (%)</i>	651 (91.4)	646 (90.7)

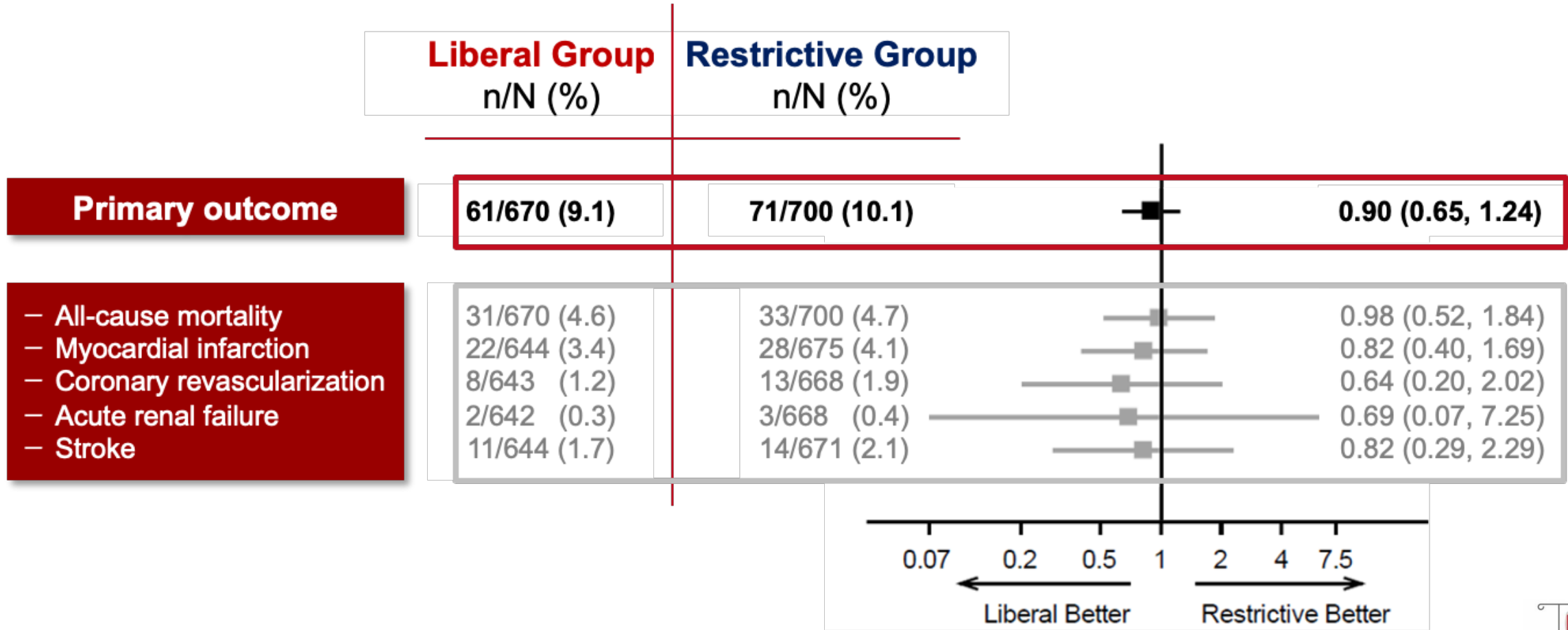
Adherence



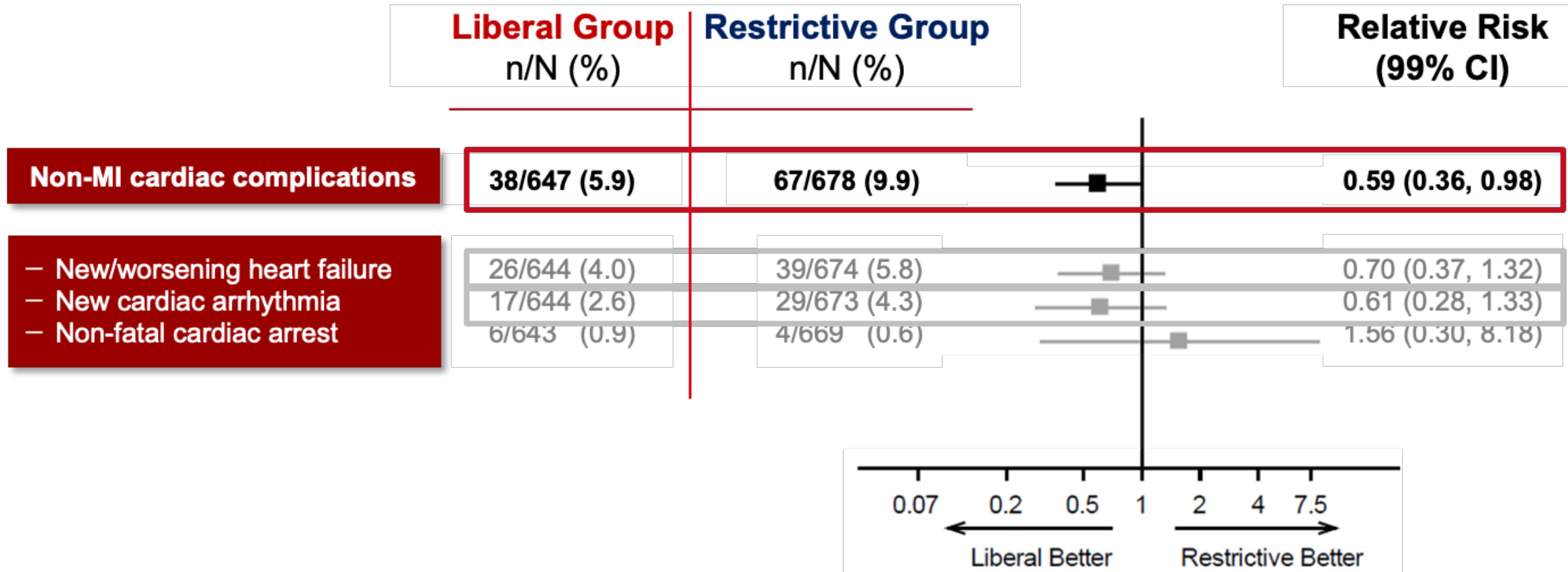
Mean Hb = 9.4 g/dL

Mean Hb = 9.0 g/dL

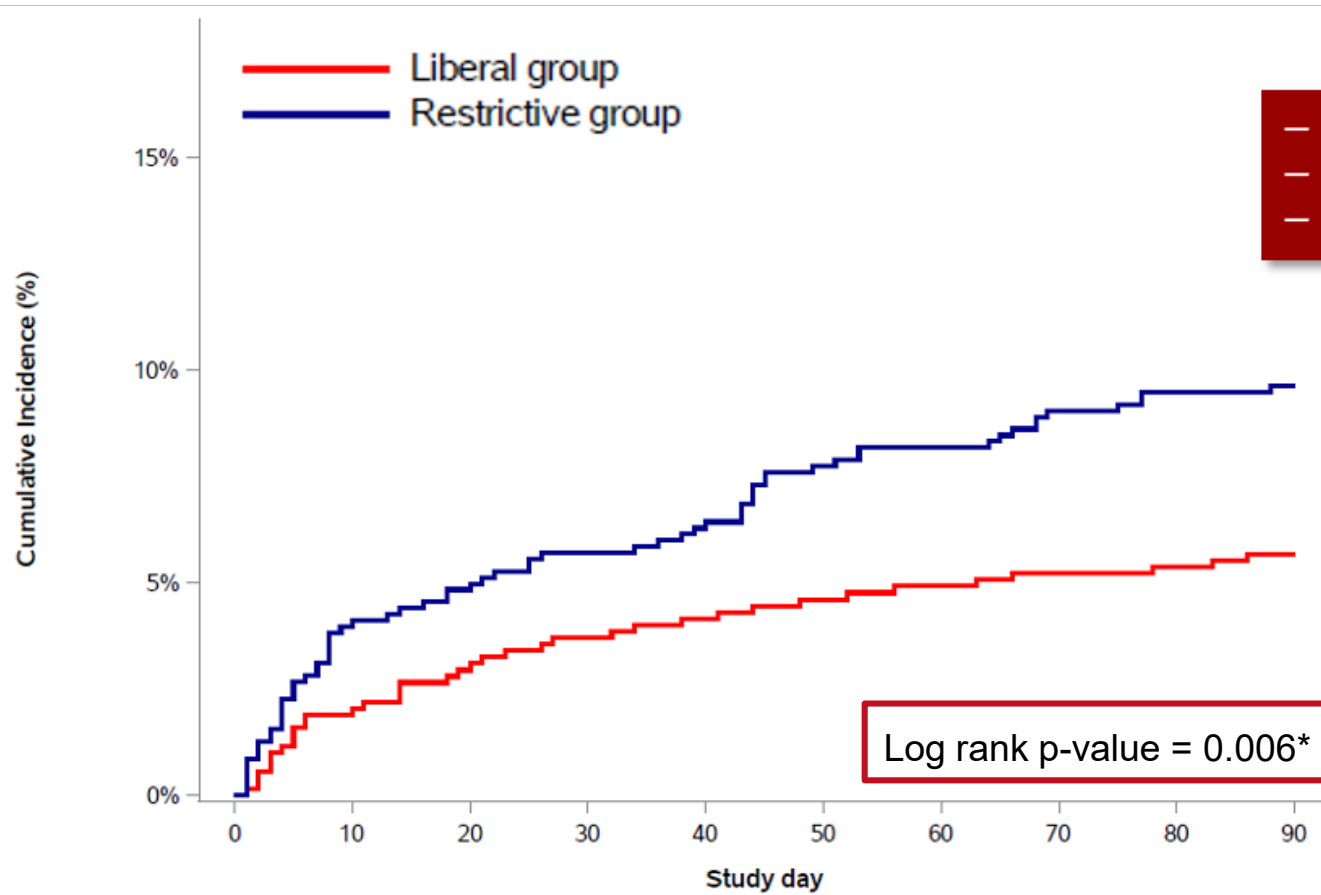
Results | Primary outcome



Results | Secondary outcome



Results | Secondary outcome



- New or worsening HF
- New cardiac arrhythmia
- Non-fatal cardiac arrest

No. at risk

	0	10	20	30	40	50	60	70	80	90
Liberal group	712	657	649	639	633	626	623	620	614	609
Restrictive group	712	668	661	653	645	634	629	621	614	611

Limitations

- The assigned strategy was not masked at the investigator level.
- The event rate for the primary endpoint was lower than anticipated, reducing the power of the trial.
- Generalizability to female patients, specialized operations may be limited.

Summary

- The TOP trial included high cardiac risk patients after major vascular and general surgery, assigned to a restrictive or a liberal transfusion strategy.
- Mortality, major ischemic events, and most secondary outcomes were similar between the groups.
- A composite outcome of heart failure and arrhythmias was more frequent in the restrictive group.

Beyond p-values

- Assumption
 - Results from this trial would be as close to the final word as possible
- Reality
 - Binary interpretations, based on statistical significance, do not come by easily in a clinical setting

Beyond p-values

- Learned the importance of nuance
 - Often, trials may generate more questions while providing some answers
- One-size-fits-all approach may not be applicable for transfusion strategies
 - Decision to transfuse high cardiac-risk patients after major surgery is nuanced
 - We cannot claim that the liberal strategy is superior for the primary outcome
 - However, the liberal strategy *may* provide cardiac outcome-related benefits
 - Needs to be confirmed in future trials

Our partners

VA



U.S. Department
of Veterans Affairs

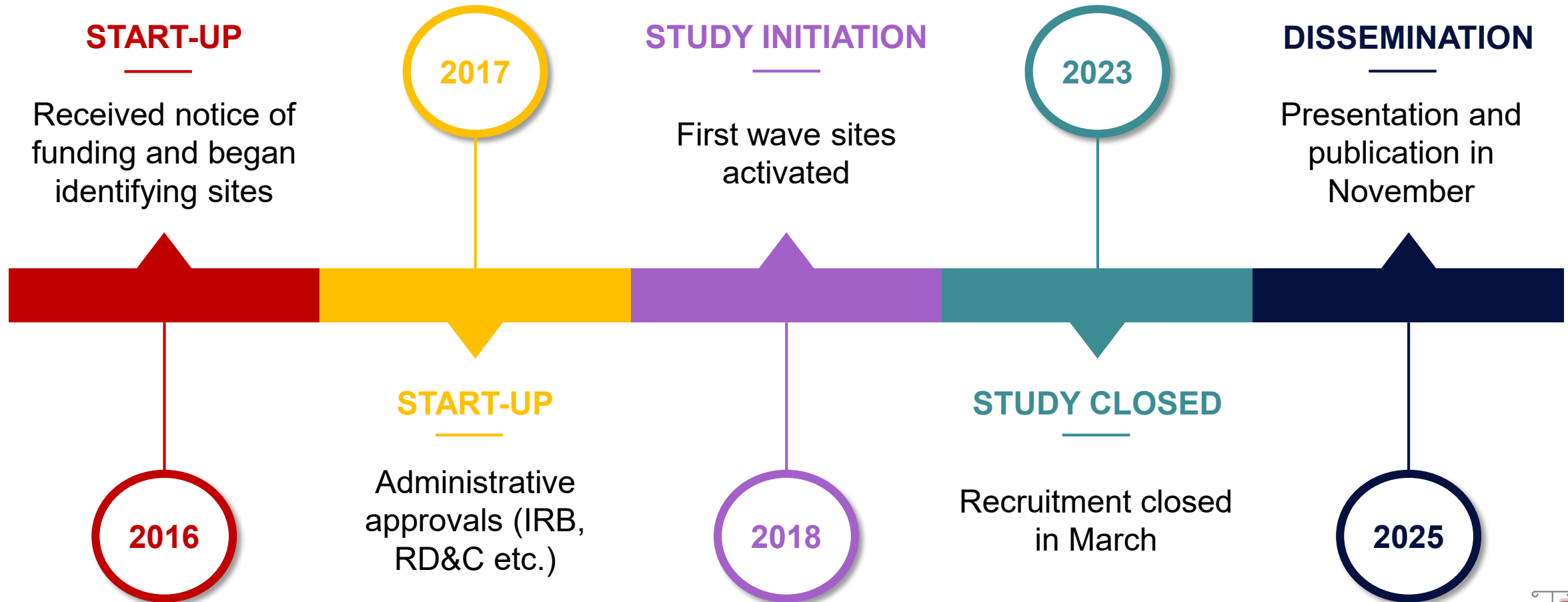
Perry Point Coordinating Center



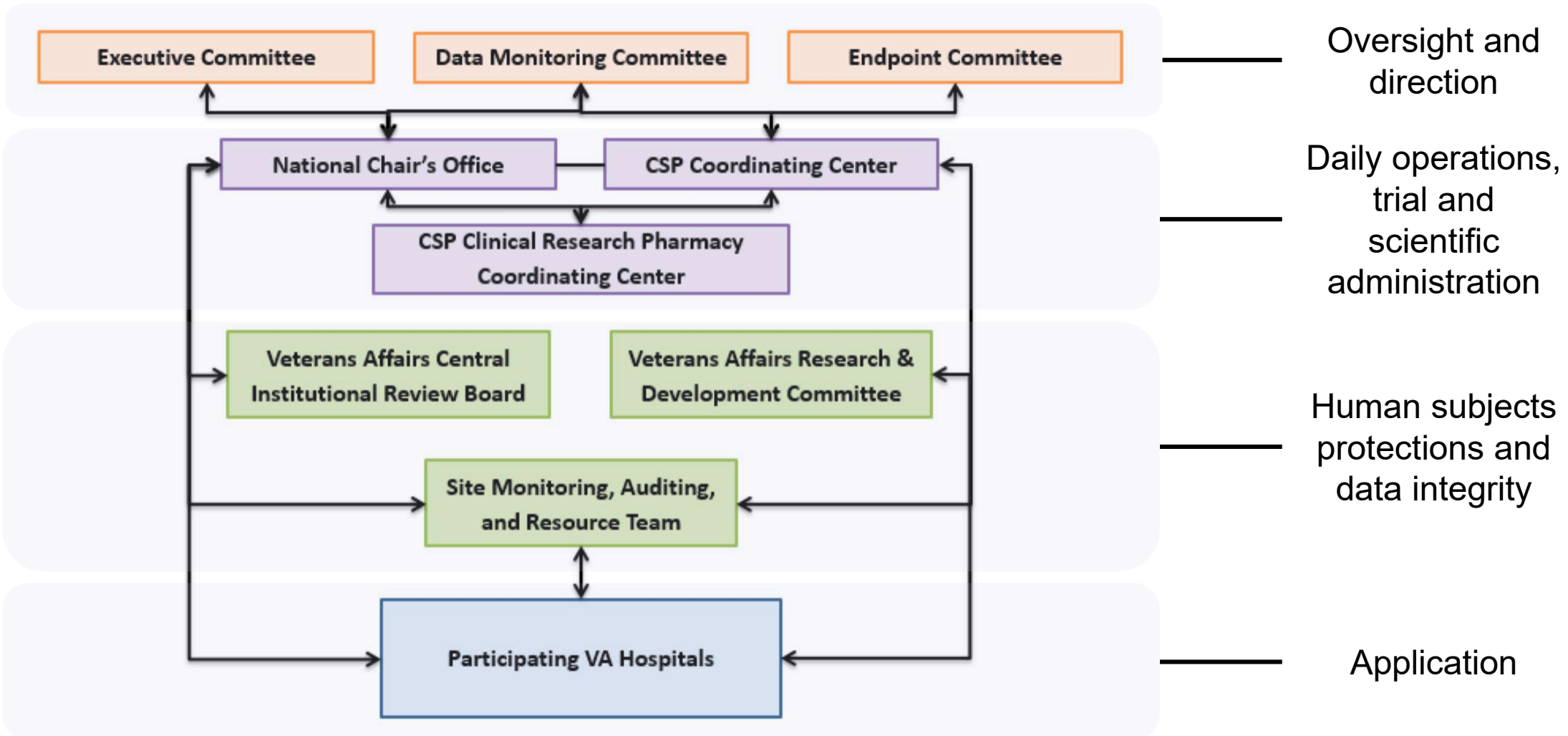
Site Monitoring and Auditing
Resource Team

Clinical Research Pharmacy
Coordinating Center

Timeline

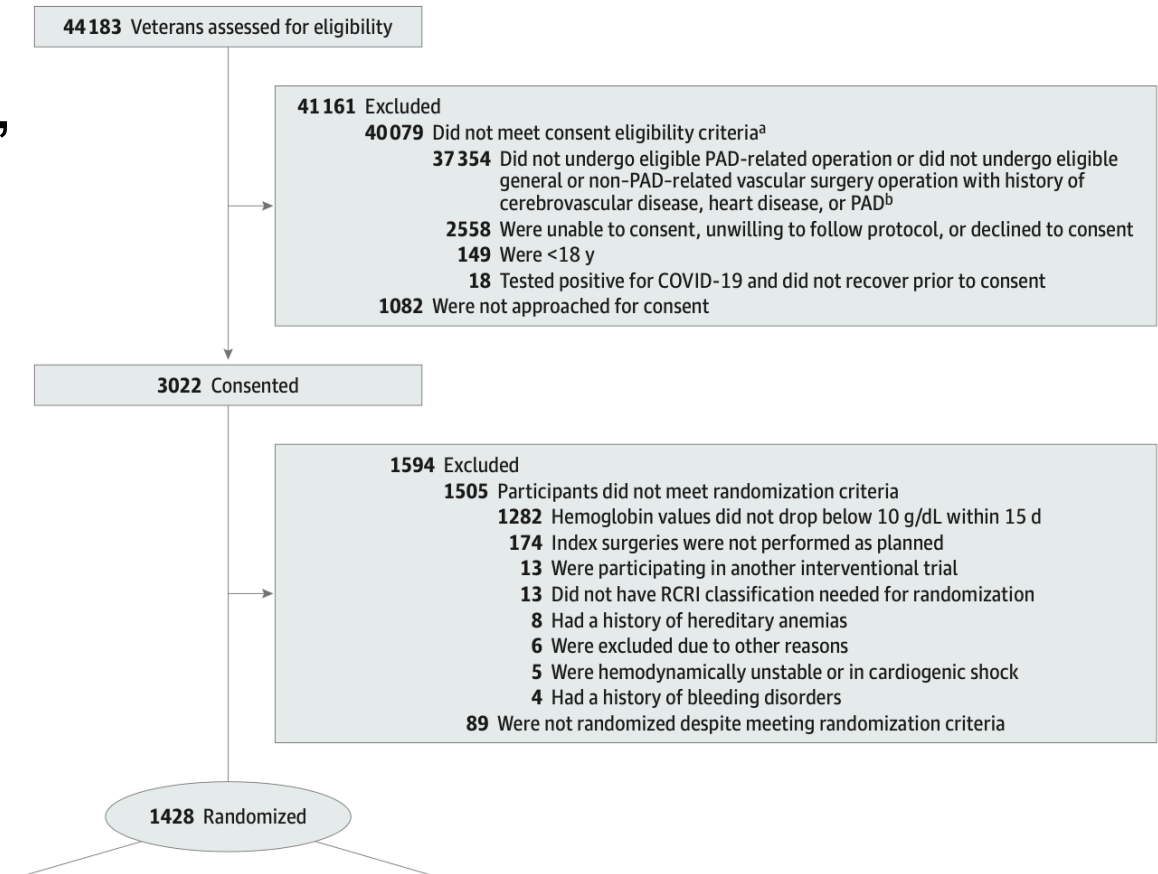


People, places, processes



Operational and logistical realities

- Strategy study
 - Intervention was not a “one and done”
- Decision points
 - Screening, consent eligibility, randomization eligibility
- Data collection





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Perry Point Coordinating Center



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JAMA | Original Investigation

Liberal or Restrictive Postoperative Transfusion in Patients at High Cardiac Risk

The TOP Randomized Clinical Trial

PMID: 41205227



Thank you!

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