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Benzodiazepine-free Cardiac Anesthesia for Reduction of Postoperative Delirium (B-Free): A Multicentre, Cluster-Randomized, Crossover Trial

Jessica Spence, MD, PhD
Assistant Professor, McMaster University
@jess_spence13

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AMERICAN COLLEGE of CARDIOLOGY

Background

- Delirium = acute disorder of cognition
  - >15% of patients **after** cardiac surgery

- Serious problem for patients and systems:
  - prolongs hospital stay
  - cost per patient >$10,229 USD
  - 30% develop PTSD
  - 32% increase in odds of in-hospital mortality

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Background

- Benzodiazepines **before and after** cardiac surgery
  - associated with delirium
  - guidelines recommend avoidance

- Benzodiazepine use **during** cardiac surgery common
  - believed to prevent intraoperative awareness
  - given to 90%

No trial has examined effect of restricting intraoperative benzodiazepines

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Study question

Does institutional policy of benzodiazepine-free cardiac anesthesia reduce incidence of delirium up to 72h after cardiac surgery?

Cluster Crossover trial design

- Selected because:
  - cardiac surgical care provided using standardized care pathways
  - anesthesiologists choose benzodiazepines (or not) based on preference
  - best way to test impact of restricting intraoperative benzodiazepines by randomly altering standard policy

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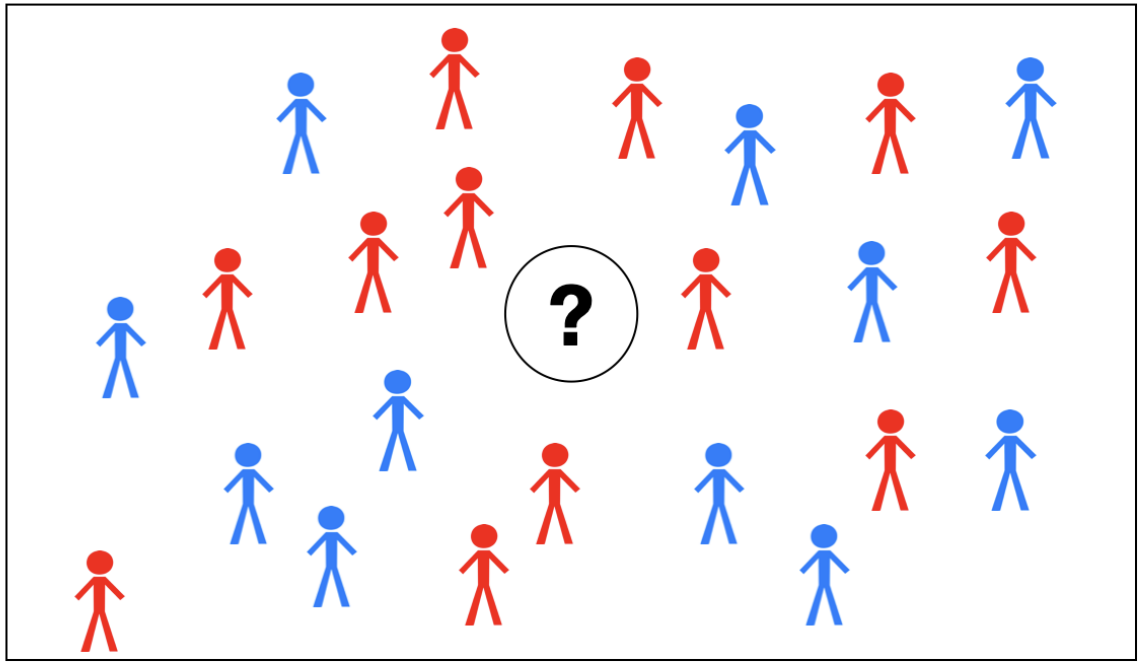
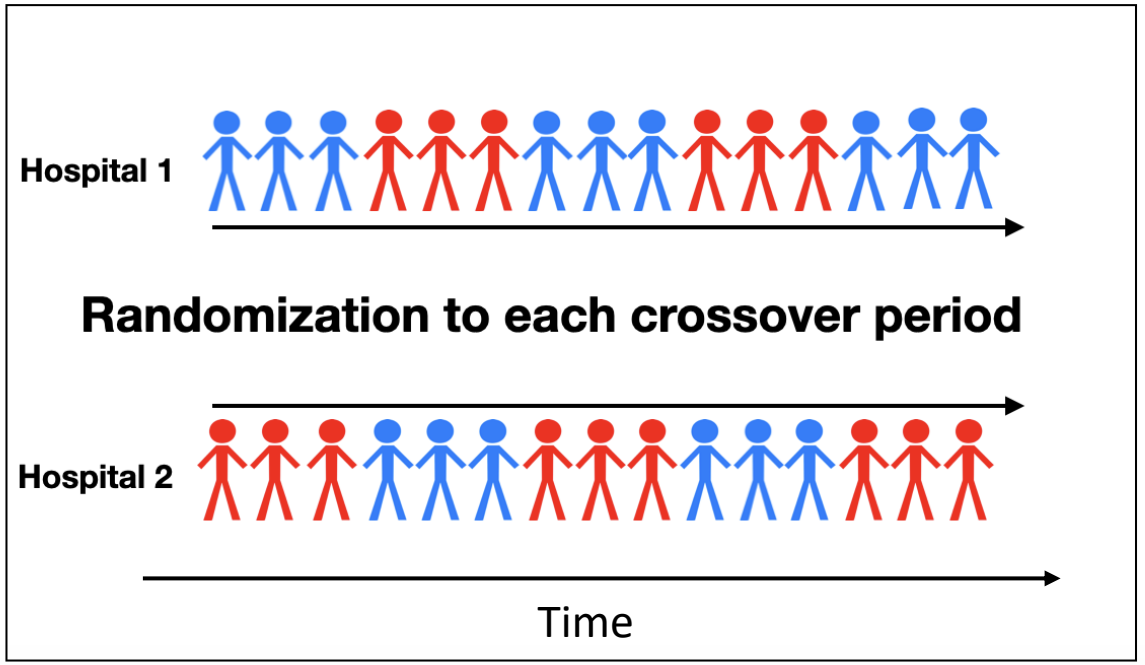
Current Practice

Haphazard



Cluster Crossover Trial

Random, Structured



Liberal

Restrictive

Study intervention arms

Restricted benzodiazepine policy	Liberal benzodiazepine policy
No routine administration of benzodiazepines	≥0.03 mg/kg Midazolam equivalent

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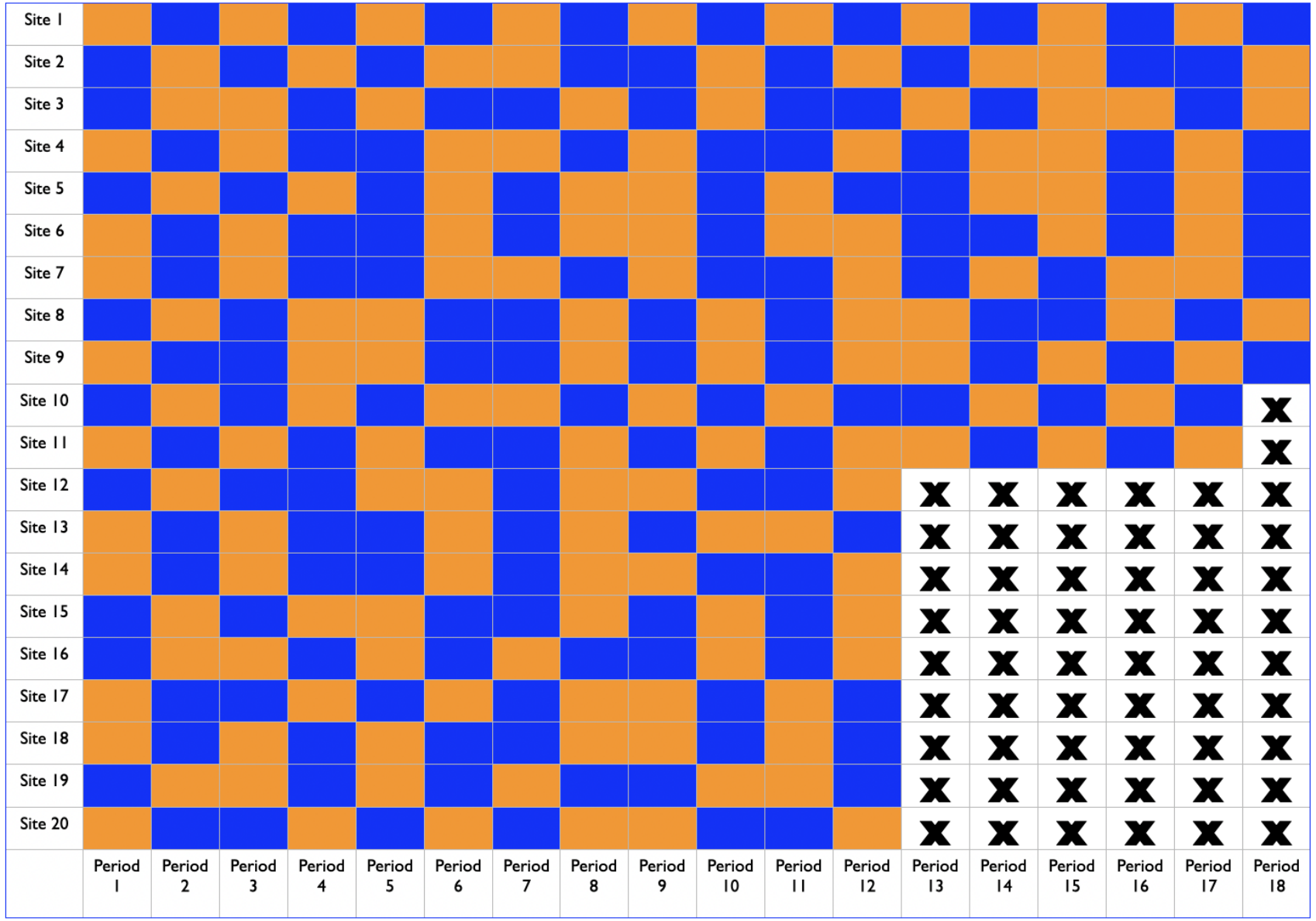
Randomization schedule

= Liberal

= Restrictive



Outcomes

- Primary outcome: delirium up to 72h after CV surgery
  - assessed by nurses in routine care
- Safety outcome: intraoperative awareness
- Post hoc outcome:
  - number of positive delirium assessments

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Analysis

- Primary outcome: logistic mixed model

- All models:
  - fixed effects term for period
  - random effects to account for within-period ICC
  - adjusted for age, sex, emergency surgery, hx ETOH, and hx of home BZD use
  - Primary analysis: ITT

Results

- 20 hospitals in Canada and US
- 19,768 patients
  - 9,827 restricted policy; 9,941 liberal policy
- Adherence to policy: **92.0%**
  - **91% restrictive, 93% liberal**

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Baseline characteristics

- Mean (SD) age: 65 (12) years
- Female patients: 27%
- Hx of home benzodiazepine use: 7%
- Hx of heavy ETOH: 5%

Surgical characteristics

- Surgical procedures
  - isolated CABG: 49%
  - isolated valve: 17%
  - other: 34%
- Emergency surgery: 8%
- Mean (SD) CPB time 116 (58) mins

Perioperative benzodiazepines

- Preoperative (within 24h): 16%
- Intraoperative
  - Restricted periods: 9%
  - Liberal periods: 93%
  - Mean (SD) dose when given (overall): 4.1 (2.5) mg
- Postoperative: 11%

Primary analysis population

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1373 (14·0)	1485 (14·9)	**0·92** (0·84 - 1·01)	0·07

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Intraoperative awareness and # positive delirium assessments

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted RR (95% CI)	*P* value
Intraoperative awareness – no. (%)	0	0	n/a	n/a
Delirium assessments positive for delirium per 72 hours – crude mean (± SD)	0·3 (1·0)	0·4 (2·2)	**0·87 (0·78, 0·98)**	0·02

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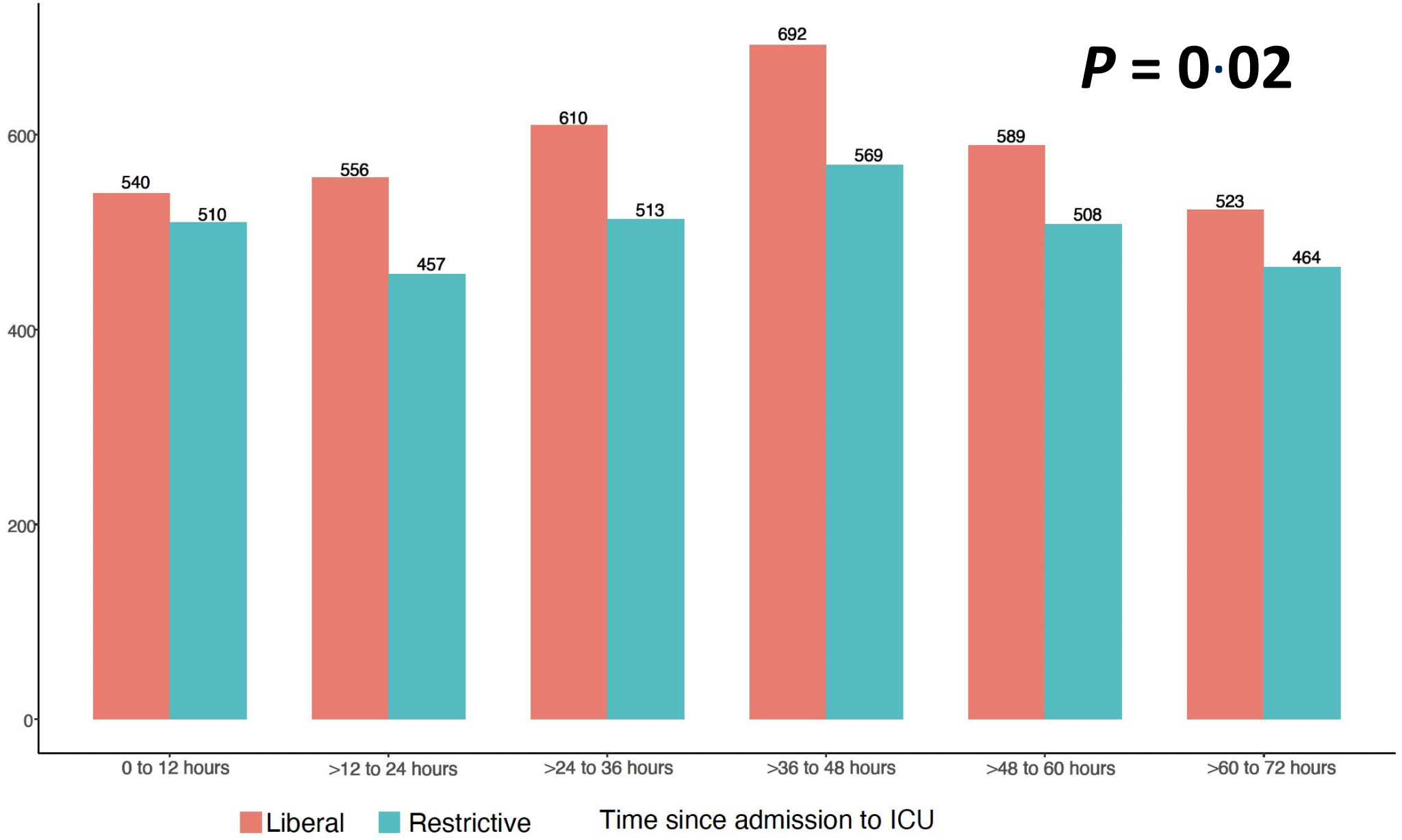
Number of positive delirium assessments



Excluding restrictive arm patients who received BZD within 24h before surgery

Outcome	Restricted benzodiazepine policy (N=8391)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1149 (13·7)	1485 (14·9)	**0·88** (0·81 - 0·97)	**0·01**

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Patients managed according to intraoperative policy

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1219 (13·7)	1372 (14·8)	**0·90** (0·82 - 0·99)	**0·02**
Removing patients who received BZD within 24h from restrictive arm				
Delirium up to 72h after cardiac surgery – no. (%)	1024 (13·4)	1372 (14·8)	**0·87** (0·79 - 0·96)	**0·005**

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Conclusions

- By ITT, restricted BZD policy did not reduce postoperative delirium
- No evidence of adverse events
  - no cases of intraoperative awareness reported
- On-policy analysis: ~10% reduction in delirium with BZD restriction
- Greater effect size the more that BZD exposure eliminated
- **Restricting benzodiazepines during cardiac surgery should be considered**

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Implications

- ~500,000 cardiac surgeries performed in US annually
  - 90% of patients receive intraoperative BZD
  - ~75,000 will develop postoperative delirium
- Institutional costs of 1 case of delirium: $10,229
- Restricting intraoperative BZD in all patients may on an annual basis in the US alone:
  - eliminate 5,000 cases of delirium
  - save institutions $51,145,000

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