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Study Design

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

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ABSTRACT

Delirium is common after cardiac surgery and is associated with adverse outcomes. Administration of benzodiazepines before and after cardiac surgery is associated with delirium; guidelines recommend

RÉSUMÉ

L'état confusionnel est fréquent après une chirurgie cardiaque et il est associé à des complications. L'administration de benzodiazépines avant et après une chirurgie cardiaque est associée à l'état con-

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minimizing their use. Benzodiazepine administration during cardiac surgery remains common because of its recognized benefits. The Benzodiazepine-Free Cardiac Anesthesia for Reduction of Postoperative Delirium (B-Free) trial is a randomized cluster crossover trial evaluating whether an institutional policy of restricting intraoperative benzodiazepine administration (ie, ≥ 90% of patients do not receive benzodiazepines during cardiac surgery), as compared with a policy of liberal intraoperative benzodiazepine administration (ie, ≥ 90% of patients receive ≥ 0.03 mg/kg midazolam equivalent), reduces delirium. Hospitals performing ≥ 250 cardiac surgeries a year are included if their cardiac anesthesia group agrees to apply both benzodiazepine policies per their randomization, and patients are assessed for postoperative delirium every 12 hours in routine clinical care. Hospitals apply the restricted or liberal benzodiazepine policy during 12 to 18 crossover periods of 4 weeks each. Randomization for all periods takes place in advance of site startup; sites are notified of their allocated policy during the last week of each crossover period. Policies are applied to all patients undergoing cardiac surgery during the trial period. The primary outcome is the incidence of delirium at up to 72 hours after surgery. The B-Free trial will enroll ≥ 18,000 patients undergoing cardiac surgery at 20 hospitals across North America. Delirium is common after cardiac surgery, and benzodiazepines are associated with the occurrence of delirium. The B-Free trial will determine whether an institutional policy restricting the administration of benzodiazepines during cardiac surgery reduces the incidence of delirium after cardiac surgery.Clinicaltrials.gov registration number: NCT03928236 (First registered April 26, 2019).

fusionnel; dans les lignes directrices, on recommande de réduire leur utilisation au minimum. L'administration de benzodiazépines pendant une chirurgie cardiaque demeure fréquente, en raison des leurs bienfaits reconnus. L'essai B-Free (*Benzodiazepine-Free Cardiac Anesthesia for Reduction of Postoperative Delirium* ou l'anesthésie sans benzodiazépine en contexte de chirurgie cardiaque pour la réduction de l'état confusionnel postopératoire) est un essai à répartition aléatoire par grappes et avec permutation, visant à évaluer si une politique institutionnelle de restriction de l'administration peropératoire de benzodiazépines (c.-à-d. que ≥ 90 % des patients ne reçoivent pas de benzodiazépines durant une chirurgie cardiaque) réduit l'état confusionnel, comparativement à une politique d'administration peropératoire libérale de benzodiazépines (c.-à-d. que ≥ 90 % des patients reçoivent ≥ 0,03 mg/kg d'équivalent du midazolam). Des hôpitaux effectuant au moins 250 chirurgies cardiaques par année sont inclus dans l'essai si leurs équipes d'anesthésie cardiaque acceptent d'appliquer les deux politiques relatives aux benzodiazépines en vertu de la répartition aléatoire et si les patients sont évalués toutes les 12 heures, en ce qui a trait à l'état confusionnel postopératoire, dans le cadre des soins cliniques habituels. Les hôpitaux mettent en œuvre la politique d'administration restreinte ou libérale de benzodiazépines durant 12 à 18 périodes de permutation de 4 semaines chacune. La répartition aléatoire de l'ensemble des périodes a lieu avant le début de l'essai à l'hôpital; les établissements sont avisés de la politique qui leur est attribuée au cours de la dernière semaine de chaque période de permutation. Les politiques sont appliquées à tous les patients qui subissent une chirurgie cardiaque durant la période de l'essai. Le critère d'évaluation principal est l'incidence de l'état confusionnel dans les 72 heures suivant l'intervention chirurgicale. L'étude B-Free inclura au moins 18 000 patients qui subiront une chirurgie cardiaque dans 20 hôpitaux en l'Amérique du Nord. L'état confusionnel est fréquent après une chirurgie cardiaque, et les benzodiazépines sont associées à la survenue de l'état confusionnel. L'essai B-Free permettra de déterminer si une politique institutionnelle de restriction de l'administration de benzodiazépines durant une chirurgie cardiaque réduit l'incidence de l'état confusionnel après une telle chirurgie.Clinicaltrials.gov registration number: NCT03928236 (First registered April 26, 2019).

Delirium is an acute neurocognitive disorder that affects 10%-50% of patients after cardiac surgery.[1] It is associated with prolonged length of stay, hospital readmission, long-term cognitive and functional decline, and death.[1-3] Delirium is such a serious problem that its incidence in the cardiovascular intensive care unit (ICU) is used as a quality metric.[4] Identification of strategies to prevent and treat delirium has been identified as a research priority. Given that more than 1 million adults undergo cardiac surgery in the US and Europe annually,[5] institutional strategies that result in even small reductions in the incidence of delirium will have important impacts on patient and healthcare system outcomes.

Evidence suggests that use of benzodiazepines in the ICU after cardiac surgery is associated with delirium,[6] and ICU guidelines now recommend avoiding their use (conditional recommendation, low quality of evidence).[6] Nonetheless, liberal use of benzodiazepines in the operating room during cardiac surgery persists in many centres.[7] A 2017 survey of Canadian cardiac anesthesiologists found that 11% of respondents never gave benzodiazepines during cardiac surgery, compared with 21% who always did. This ongoing use is driven mainly by the favourable amnestic and hemodynamic properties of benzodiazepines and the belief that benzodiazepines may help prevent intraoperative awareness, during which cardiac surgery patients are at greater risk.[7] However, practice varies markedly across centres and individual anesthesiologists,[7,8] with some administering benzodiazepines to all cardiac surgery patients and some never using benzodiazepines as part of a cardiac anesthetic. A recent analysis of

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See page 698 for disclosure information.

65,508 cardiac surgery patients found that variation in benzodiazepine administration was 54.7% attributable to institution, 14.7% attributable to the primary attending anesthesiologist, and only 30.5% attributable to patient factors.[8] This wide variation in practice is abetted by a lack of reliable data about the effect of intraoperative benzodiazepine use on postoperative delirium, and the limitations in the evidence about their effect on intraoperative awareness. A randomized trial is required to determine the optimal approach to benzodiazepine administration during cardiac anesthesia. We are conducting this trial to address the following question: Does a policy of restricted intraoperative benzodiazepine use during adult cardiac surgery, compared to a policy of liberal intraoperative benzodiazepine use, reduce the incidence of postoperative delirium? Our results will guide cardiac anesthesia practice and could improve the outcomes of the millions of patients per year who have cardiac surgery worldwide.

Rationale for a Cluster-Randomized Trial

Individual-patient efficacy trials are useful to establish the clinical efficacy of an intervention among a carefully selected population under optimal conditions following detailed protocols. However, such trials do not address questions of clinical effectiveness, which focus on how well an intervention or policy works in clinical practice.

Cardiac surgery is provided in specialized institutions performing high volumes of surgery, to reduce complications and increase efficiency. The surgical care of patients in these high-volume cardiac surgery centres is undertaken using standardized procedures that optimize outcomes, such as standard preoperative assessment and pre- and postoperative care pathways. Because cardiac surgical care is delivered through standard institutional policies, addressing the question of whether an institutional policy of limiting benzodiazepine use during surgery would reduce the incidence of delirium is appropriate. Testing the effects of different institutional policies mandates a pragmatic trial done with randomization of institutions rather than patients. Thus, this study uses a cluster-randomized crossover design, an approach that is methodologically rigorous and tests the effect of a change in standard policy, as used in routine clinical care (Fig. 1).

Trial Objectives

The primary objective of the **B**enzodiazepine-**Free** Cardiac Anesthesia for Reduction of Postoperative Delirium (B-Free) trial is to evaluate the impact of an institutional policy of limited benzodiazepine use, as compared to that of a policy of liberal benzodiazepine use, during cardiac surgery, on the incidence of delirium up to 72 hours after cardiac surgery. The secondary objectives of the B-Free trial are to evaluate the impact of these policies on ICU length-of-stay, hospital length-of-stay, and all-cause in-hospital mortality.

Methods

Trial design

The B-Free trial is a 20-centre randomized cluster crossover trial of 18,000 patients undergoing cardiac surgery. Centers in North America are randomized to apply both the restrictive and the liberal intraoperative benzodiazepine policies at random. The trial is registered at clinicaltrials.gov (NCT03928236). The **S**tandard **P**rotocol **I**tems: **R**ecommendations for **I**nterventional **T**rials (SPIRIT) checklist for this design is provided in Supplemental Appendix S1.

Trial population

We include tertiary cardiac surgical centres completing on average $\geq$ 250 cardiac surgical cases annually if the following are true: (i) $\geq$ 95% of the hospital's cardiac anesthesia group agrees to manage patients per the study benzodiazepine use policy in place during each crossover period; and (ii) patients are routinely assessed for postoperative delirium at least every 12 hours in the ICU after cardiac surgery as a part of routine clinical care using either the Confusion Assessment Method-ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC). All patients undergoing cardiac surgery at an enrolled site during the trial period are included in data collection; percutaneous procedures (eg, transcutaneous valve procedures) and secondary operations during the same admission are excluded. Patients are tracked through monitoring of surgical rosters and postoperative admissions to the cardiac surgical ICU.

Randomization and blinding

We randomize sites to 1 of the 2 policies to be used by all cardiac anesthesiologists for the duration of each crossover period, with randomization blocked in periods of 2, to minimize period effects. An independent statistician randomizes each site to complete 12-18 crossover periods. Randomization for all periods takes place in advance of site startup, but sites are only notified of the subsequent period's policy during the last week of each crossover period (Fig. 2).

Cardiac surgery ICU nurses are blinded to the intraoperative benzodiazepine policy. They use standardized assessment tools to determine if delirium is present as part of routine care. Cardiac surgeons and anesthesiologists are not blinded to patients' treatment allocation, as this may compromise patient care.

Trial interventions

The B-Free trial compares 2 hospital-based cardiac anesthesia policies, both of which fall within the standard of care. Both policies allow deviations to occur when mandated by patient condition according to anesthesiologist discretion. We expect that $\geq$ 90% of patients will be treated according to the assigned policy, due to appropriate deviations, as described in Table 1.

Benzodiazepine administration before and after surgery is minimized during both policy implementation periods in accordance with current guidelines.[6,9] Recognized exceptions to this approach include administration for patients who are benzodiazepine dependent, are alcohol dependent, or are having seizures. We promote knowledge translation of the guidelines through e-mail reminders and posters displayed on cardiac surgery and cardiology wards.

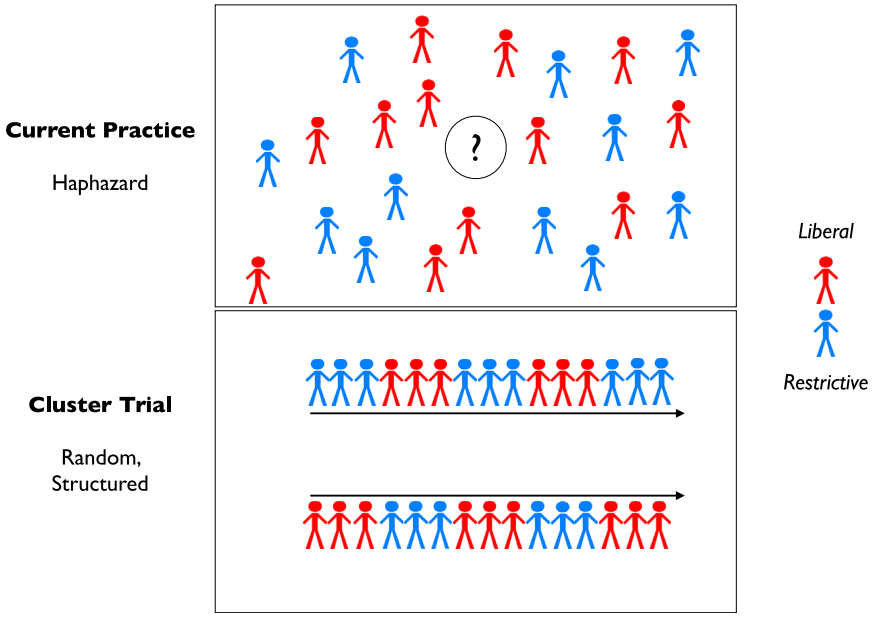

Figure 1. Study schematic. The top part of the diagram presents benzodiazepine administration in routine clinical practice. The bottom part of the diagram presents benzodiazepine administration as it occurs in the **B**enzodiazepine-**Free** Cardiac Anesthesia for Reduction of Postoperative Delirium (B-Free) trial. **Blue figures** represent use of a restricted approach to intraoperative benzodiazepine administration. **Red figures** represent use of a liberal approach to intraoperative benzodiazepine administration.

Duration of treatment period

The duration of each intervention period is 4 weeks, and all 20 sites complete between 12 and 18 crossover periods, as determined per local feasibility.

Trial outcomes

The primary outcome is delirium occurring within 72 hours after surgery, as measured in routine clinical care using either the CAM-ICU[10] or the ICDSC.[11] The secondary outcomes are as follows: (i) ICU length-of-stay, defined as the number of hours in the cardiac surgical ICU following index cardiac surgery until the initial ICU discharge; (ii) hospital length-of-stay, defined as the number of days from index cardiac surgery until initial hospital discharge; (iii) in-hospital mortality, defined as death from any cause after the index cardiac surgical procedure until the initial hospital discharge. Consistent with our pragmatic approach, all trial data are obtained as part of routine clinical care and are documented in hospital medical records. As patient-reported outcomes and quality of life are not normally documented in patient charts, we are unable to evaluate these outcomes.

Duration of follow-up

Patients are followed until hospital discharge after their index cardiac surgery. Patients who remain in the hospital at 4 months after the last site has completed the last crossover period will be censored at that time.

Data management

Study personnel collect data from hospital administrative databases, chart reviews, and/or electronic medical records. Data collected include key baseline characteristics, such as demographics, details of surgery, postoperative delirium, and pre- and postoperative medications. Study personnel at most participating sites record data that they submit to a secure web-based computerized database (ie, TrialMaster). For sites unable to manually enter data, patient data are downloaded directly from the site's administrative data system. A secure file transfer protocol is created for electronic upload and transfer of the downloaded data. The project office team then reviews and imports these data into the database. Patients are identified using a unique numeric code, and all patient data are anonymized to ensure patient confidentiality. Data validity checks are programmed in the database and are monitored by data management assistants from the project office through multilevel data validation.

Impact of the COVID-19 pandemic

On 2 occasions (March 17, 2020 to September 13, 2020; November 9, 2020 to May 2, 2021) during the COVID-19 pandemic, the steering committee placed the B-Free trial on hold for the following reasons: (i) mandated cancellation of elective surgeries meant that only a small number of patients were undergoing cardiac surgery; (ii) as a result of cancellations, the patients who were undergoing cardiac surgery had a condition of greater acuity, with a different baseline risk of postoperative delirium; and (iii) participating in the trial may increase the stress already experienced by anesthesiologists related to their risk of exposure to and infection with COVID-19.

To ensure study integrity, we stipulated the following requirements for sites to resume the trial: (i) institutional approval to conduct B-Free trial research; (ii) case volume of at least 80% of normal and with a demographic and case mix that approximated the pre-COVID period; (iii) an expectation

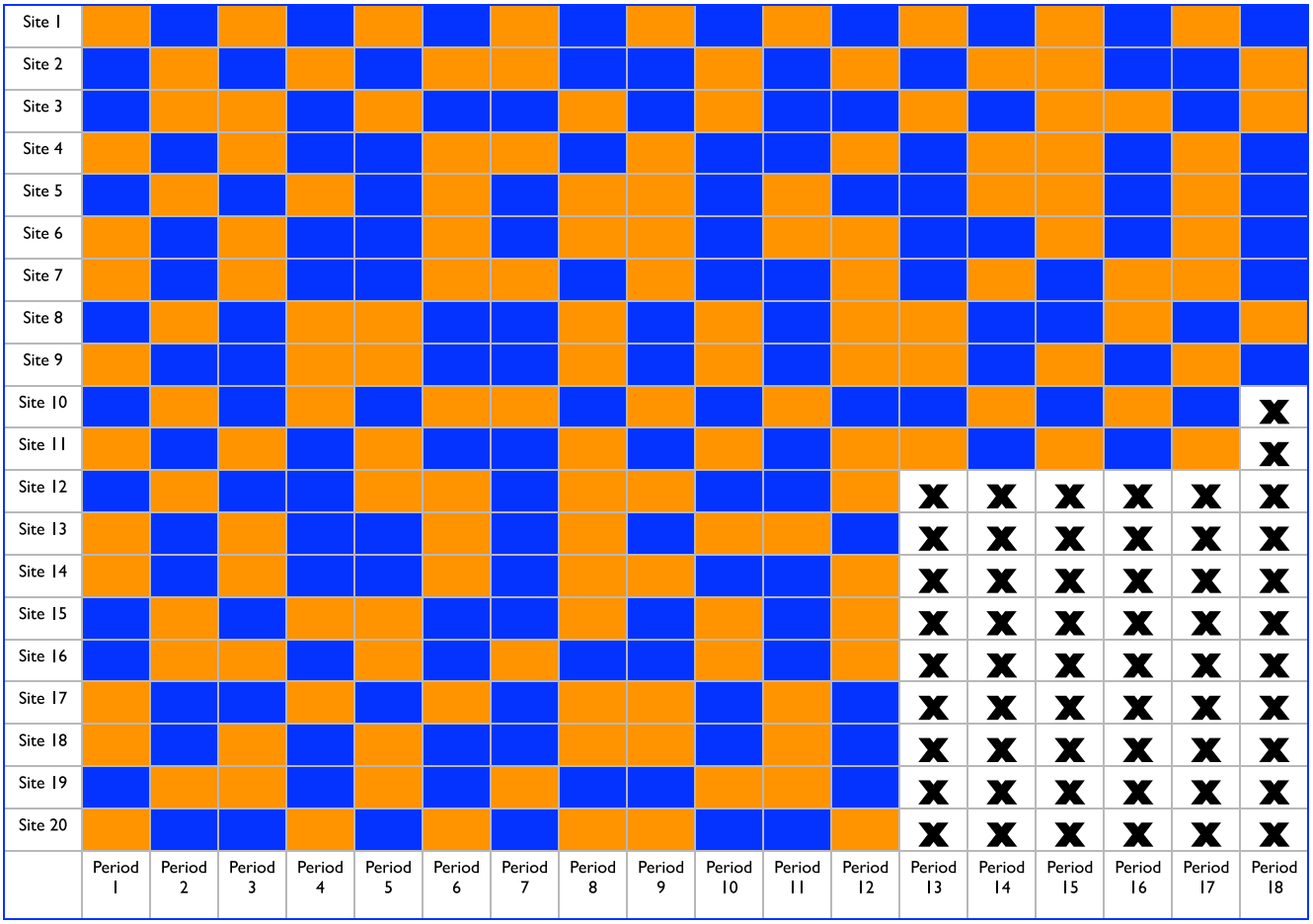

Figure 2. Sample randomization schedule. This diagram represents a possible randomization schedule for 20 clusters completing between 12 and 18 crossover periods. **Blue squares** represent periods during which the restricted benzodiazepine policy is applied. **Orange squares** represent periods during which the liberal benzodiazepine policy is applied. **"X" squares** represent periods in which a site is not participating in the trial.

that case volume would be maintained or increased over the subsequent period; (iv) the ability to conduct trial activities requiring someone on site; and (v) agreement of site cardiac anesthesiology groups to implement B-Free trial intervention arm policies according to randomization.

As of March 7, 2022, all 20 sites had resumed the trial, and since that date, no sites have had to pause trial activities for the reasons described above.

Statistical considerations

(i) Initial sample size. Based on our initial sample size calculation, we required 16 hospitals with an overall average annual case volume of 1000 patients to complete 12 crossover periods of 4 weeks each, to achieve statistical power > 80%. This number of clusters and patients would allow the detection of a relative risk reduction of 15%, based on our assumptions of a control delirium rate of 15%, an intracluster correlation coefficient (ICC) of 0.02, an inter-period correlation (IPC) of 0.5*ICC (ie, 0.01), and a type I error of 5%.

The ICC describes the similarity in outcome within a cluster, and the variance in outcome that exists across clusters. The ICC has been shown previously to be related to outcome prevalence in clustered, binary data.[12] We thus used local delirium rates to estimate an ICC of 0.02, based on values determined by Gulliford et al.[12] The IPC coefficient describes the variance in outcome between individuals from the same cluster across different periods; typically, obtaining estimates of the IPC is difficult.[13] As previously described, we used an assumed value that was half the magnitude of the ICC, consistent with the recommended standard.[12,14,15]

(ii) Interim analysis. An independent data safety monitoring board performed an interim analysis to assess efficacy and safety, which was completed on May 25, 2022, based on data obtained as of May 9, 2022. The interim analysis was initially planned for when 50% of data was available, but due to scheduling conflicts and data entry delays, it was completed when 70% of patients had been enrolled. A modified Haybittle-Peto approach was used to evaluate both the primary outcome of delirium incidence and the secondary outcome of in-hospital mortality. The data safety monitoring board was instructed to recommend early trial termination if a reduction in delirium occurred in favour of either policy that met the statistical criterion of 3 standard deviations (see Supplemental Appendix S2).

Table 1. Description of intervention and control arm policies

The "restricted benzodiazepine policy" arm	The "liberal benzodiazepine policy" arm
1. No routine use of any intraoperative benzodiazepines. 2. Accepted benzodiazepine use in the case of seizure, alcohol withdrawal, severe anxiety, history of awareness during anesthesia, or known benzodiazepine dependence. 3. Accepted benzodiazepine use in patients who are hemodynamically unstable and/or have cardiac anatomy that puts them at high risk of hemodynamic deterioration on induction of anesthesia using other agents.	1. Intraoperative administration of the equivalent of at least 0.03mg/kg midazolam ideal body weight (60 kg in women, 70 kg in men) equivalent to all patients undergoing cardiac surgery. 2. Any benzodiazepine may be given intraoperatively. 3. Accepted avoidance of benzodiazepines in patients who have contraindications to the administration of these medications (eg, documented allergy, previous adverse reaction).

(iii) Trial adaptation. Because of concerns about the impact of the COVID-19 pandemic on cardiac surgery case volumes, and the uncertainty of the assumptions used in our original sample size estimate, a decision was made to perform a blinded sample size re-estimation (bSSR) based on data from 11,222 patients. We did this at the time of our interim analysis, without unblinding the treatment effect. The purpose was to re-evaluate the original sample-size assumptions to extend the duration of the trial if needed to maintain statistical power at 80%. Sample size re-estimation was based on the observed incidence of delirium and the ICC. Further detail regarding the approach to and results of our trial adaptation will be published in a separate statistical methods article.

(iv) Modified sample size. Based on the results of our adaptive analysis, our modified sample size includes 9 hospitals completing 18 periods, 2 hospitals completing 17 periods, and 9 hospitals completing 12 periods, with an overall average of 900 cardiac surgery patients per cluster and a control delirium rate of 17%, assuming an ICC of 0.06, an IPC of 0.03, and a type I error of 5% (Table 2).

(v) Data analysis

Analysis populations. The intention-to-treat population will include all adult (aged $\geq$ 18 years) patients who underwent cardiac surgery during times when the trial was active at each included cluster.

Main analysis. The primary analyses will be based on the intention-to-treat principle—that is, participants will be analyzed according to the policy in use when they underwent surgery, regardless of whether they were managed according to the policy. We will report the incidence and dose of benzodiazepine administered according to treatment allocation. Standard methods will be used to report tabular and graphical summaries, as appropriate, for continuous and categorical variables. Summaries of continuous variables will include the number of subjects (N), mean (standard deviation), and median (25th and 75th percentiles). Frequency distributions (N and %) will be reported for categorical data.

All analyses will take place at the individual-patient level. Analyses will be carried out comparing event rates in patients managed during the restricted-benzodiazepine-policy periods compared to the liberal-benzodiazepine-policy periods. Primary and secondary outcomes will be compared between treatment allocation using a logistic mixed model for binary outcomes and a linear mixed model for continuous outcomes, accounting for within-period intracluster correlation and an exponential decay in the strength of correlation over time, so as to control for possible differences in outcome across centres and within centres across different temporal periods.[16,17] We will report odds ratios and 95% confidence intervals. We will claim statistical significance for treatment effectiveness if $P < 0.05$ for the primary outcome. For sensitivity analyses, we will assess for treatment effect heterogeneity across periods, clusters, and clusters with a different number of periods for the primary outcome. We have not prespecified per protocol analyses, as this would abnegate the balance of prognosis achieved through randomization and yield unreliable results that may affect the interpretation of the primary analysis. We will use SAS 9.4 for UNIX (SAS Institute, Cary, NC) or other validated software, for all analyses.

Economic analysis. Restricting benzodiazepines during cardiac surgery does not meaningfully change the cost of cardiac anesthesia or perioperative care. If the B-Free trial demonstrates superiority for the outcome of delirium when a restricted-benzodiazepine approach is used, it will clearly be a

Table 2. Assumed, observed, and recalculated sample size calculations

	RRR, %	Average cluster size	Control delirium incidence	# periods	ICC	IPC	Total n (projected)	# clusters	Alpha, %	Power
Assumed	15	1000	0.15	12	0.02	0.01	16,000	16	5	0.8
Observed	—	750	0.17	12	0.06	0.03	15,000	20	—	0.70
Recalculated	15	1000	0.17	12	0.06	0.03	20,000	20	5	0.74*
	15	900	0.17	15	0.06	0.03	18,000	20	5	0.81†
	15	1250	0.17	18	0.06	0.03	22,500	20	5	0.88‡

RRR, relative risk reduction; ICC, intracluster correlation coefficient; IPC, inter-period correlation; RRR, relative risk reduction.

* Reflects statistical power with pre-pandemic case volumes and observed ICC/IPC.

† Proposed adaptation. Number of crossover periods reflects the average across all clusters (ie, 18 in 9 sites; 17 in 2 sites; 12 in 9 sites).

‡ Statistical power using observed ICC/IPC if all sites completed 18 periods.

Table 3. Prespecified subgroups and associated hypotheses to explain heterogeneity in effect of intraoperative benzodiazepine policy on postoperative delirium

Subgroup	Hypothesized effect of intraoperative benzodiazepine policy on delirium
Female sex	Restricted intraoperative benzodiazepine administration will have a greater absolute but similar relative risk reduction in female, compared to male, patients
Age*	Restricted intraoperative benzodiazepine administration will be associated with a greater relative risk reduction in older, compared to younger, patients
Benzodiazepine dose†	Higher doses of benzodiazepine given during the liberal intraoperative benzodiazepine policy periods will be associated with a higher relative risk, compared to that with lower doses
Emergency surgery	Restricted intraoperative benzodiazepine administration will have the same relative risk reduction but a greater absolute risk reduction in patients undergoing emergency, compared to scheduled, surgery
Patients with home benzodiazepine use or alcohol abuse	Restricted intraoperative benzodiazepine administration will be associated with a relative risk increase
Centres assessing delirium using the CAM-ICU as compared to the ICDSC	Restricted intraoperative benzodiazepine administration will have a greater absolute, but similar relative, risk reduction in centres assessing delirium using the CAM-ICU, as compared to the ICDSC

CAM-ICU, confusion assessment method-intensive care unit; ICDSC, intensive care delirium screening checklist.
* Grouped in tertiles.
† Dichotomized as $\geq$ 5 mg or $<$ 5 mg.

lower cost strategy,' although this is not consistent with the language typically used for economic analyses. Therefore, an economic analysis is not planned.

Subgroup analyses. We will evaluate the following subgroups of interest: sex, age, benzodiazepine dose, urgent/emergent surgery, and patients with a history of benzodiazepine use or alcohol abuse, either separately or together. At the cluster-level, we will evaluate the subgroup of hospitals that assess for delirium using the CAM-ICU, as compared to the ICDSC. The subgroup analyses will be conducted using tests for interactions in a mixed regression model for the primary and secondary outcomes. We will use the **I**nstrument for Assessing the **C**redibility of **E**ffect **M**odification Analyses (ICEMAN) criteria to assess the credibility of each subgroup.[18] We will consider subgroups to be significant if they are assessed to have moderate or high credibility. Our a priori hypotheses for these subgroups are described in Table 3.

Trial organization

Study coordinating centre. The Population Health Research Institute (PHRI; Hamilton, Ontario, Canada) is the coordinating centre for this trial and is responsible for central randomization, the trial database, data consistency checks, data analyses, and coordination of participating centres worldwide. The steering committee is responsible for the design, execution, analysis, and reporting of the study. This committee regularly convenes by video conference to address issues and monitor study progress, execution, and management. The steering committee includes the principal investigators, key investigators with specific expertise in delirium, bioethics, and statistics, and 2 patient partners. The steering committee holds the primary responsibility for publication of the study results on behalf of the B-Free trial investigators. Supplemental Appendix S3 describes the trial organizational structure.

Ethics. The study is conducted in accordance with the principles of good clinical practice (GCP), all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki, including, but not limited to the following:

- institutional review board / research ethics board review and approval of study protocol and any subsequent amendments; and
- a modified consent process approved by the institutional review board.

Waiver of individual patient consent. The cluster design challenges conventional approaches to clinical research because patients cannot choose to avoid either the intervention or consent for the study, because the intervention is applied at the level of the healthcare environment and not that of the patient. The B-Free trial evaluates 2 different cardiac anesthesia policies related to the use of benzodiazepines (restricted vs liberal intraoperative administration) that are applied at the level of a centre. Centres were only included if physician equipoise was present regarding the benzodiazepine policies being tested in this study. The different approaches to the use of benzodiazepines, embodied in the 2 study policies being evaluated, are both of minimal risk and are commonly used in Canada and other countries.[10] Within the B-Free trial, we are standardizing, rather than changing, routine clinical care, such that we can evaluate the impact of policy changes on patient outcomes at the level of an institution. Before study initiation, we obtained a waiver of individual patient consent at each institution, according to criteria proposed by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[19] This study fulfills these criteria in that the following ways: (i) The study poses minimal risk to patients; (ii) Waiver of consent will not adversely affect patient rights and welfare; (iii) Carrying out the research would be impracticable if prior consent is required; and (iv) Patients and/or families will be provided with information about the study using an information letter and/or a poster in the ICU waiting areas.

Dissemination

To disseminate our findings, we will present study results at national and international conferences and publish primary and substudy results in peer-reviewed high-impact journals.

Discussion

More than 1 million adults per year undergo cardiac surgery. Of these, more than 200,000 will develop postoperative delirium,[1] which is associated with cognitive decline, functional decline, and death. Benzodiazepines are medications that have been associated with delirium but continue to be used routinely as part of a cardiac anesthetic because of their pharmacologic profile, as well the fact that they have been incorporated into individual and institutional routine practice. The B-Free trial will determine whether restriction of benzodiazepine use during cardiac surgery decreases the incidence of postoperative delirium and will inform cardiac anesthesia practice going forward.

Trial progress

This paper is based on the most recent version of the study protocol (ie, version 5.0). The first site commenced enrollment on November 18, 2019. Up to the date of December 11, 2022, we had enrolled 15,286 patients across 20 North American centres, which have applied the restrictive and liberal policies over 18 crossover periods. We have built a large investigator group that includes both the banner authors and those listed in Supplemental Appendix S4 as "B-Free Investigators."

Ethics Statement

The study is conducted in accordance with the principles of GCP) all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki, including, but not limited to the following: 1) institutional review board / research ethics board review and approval of study protocol and any subsequent amendments; and 2) a modified consent process approved by the institutional review board.

Patient Consent

Before study initiation, we obtained a waiver of individual patient consent at each institution, according to criteria proposed by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[19]

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.06.001.