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Restricted *versus* liberal intraoperative benzodiazepine use in cardiac anaesthesia for reducing delirium (B-Free Pilot): a pilot, multicentre, randomised, cluster crossover trial

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Abstract

Background: Delirium is common after cardiac surgery and is associated with adverse outcomes. Perioperative benzodiazepine use is associated with delirium and is common during cardiac surgery, which may increase the risk of postoperative delirium. We undertook a pilot study to inform the feasibility of a large randomised cluster crossover trial examining whether an institutional policy of restricted benzodiazepine administration during cardiac surgery (compared with liberal administration) would reduce delirium.

Methods: We conducted a two-centre, pilot, randomised cluster crossover trial with four 4 week crossover periods. Each centre was randomised to a policy of restricted or liberal use, and then alternated between the two policies during the remaining three periods. Our feasibility outcomes were adherence to each policy (goal ≥80%) and outcome assessment (one delirium assessment per day in the ICU in ≥90% of participants). We also evaluated the incidence of intraoperative awareness in one site using serial Brice questionnaires.

Results: Of 800 patients undergoing cardiac surgery during the trial period, 127/800 (15.9%) had delirium. Of these, 355/389 (91.3%) received benzodiazepines during the liberal benzodiazepine periods and 363/411 (88.3%) did not receive benzodiazepines during the restricted benzodiazepine periods. Amongst the 800 patients, 740 (92.5%) had ≥1 postoperative delirium assessment per day in the ICU. Of 521 patients screened for intraoperative awareness, one patient (0.2%), managed during the restricted benzodiazepine period (but who received benzodiazepine), experienced intraoperative awareness.

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Conclusions: This pilot study demonstrates the feasibility of a large, multicentre, randomised, cluster crossover trial examining whether an institutional policy of restricted *vs* liberal benzodiazepine use during cardiac surgery will reduce postoperative delirium.
Clinical trial registration: NCT03053869.

Keywords: awareness; benzodiazepines; cardiac anaesthesia; delirium; pilot study; pragmatic; randomised cluster crossover

Editor's key points

- Delirium occurs in 15–20% of patients in the ICU after cardiac surgery, and is associated with significant morbidity and mortality.
- Use of benzodiazepines during surgery may contribute, but there is uncertainty as to whether or not benzodiazepines should be used, as shown by the large variation in clinical practice.
- The B-Free Pilot trial was designed as a multicentre cluster crossover trial addressing the feasibility restricted *vs* liberal benzodiazepine administration during cardiac surgery.
- The trial demonstrated adherence to both intervention arm policies, ability to collect delirium assessments as part of routine clinical care, and no increase in intraoperative awareness using the restricted intraoperative benzodiazepine approach.
- The clinical acceptability of both approaches supports equipoise in practice and the feasibility of a large trial.

Delirium affects 15–25% of adults after cardiac surgery,[1,2] and is associated with prolonged length of stay (LOS),[3] hospital readmission,[3] long-term cognitive[4] and functional decline,[3,4] and death.[5] Observational studies have suggested an association between perioperative benzodiazepine administration and delirium in both cardiac[6] and noncardiac surgery populations,[7,8] and in mechanically ventilated patients in the ICU.[9] A recent meta-analysis of RCTs comparing benzodiazepines with dexmedetomidine for ICU sedation demonstrated a trend towards increased delirium with benzodiazepine sedation, with a relative risk (RR) of 1.23 (95% confidence interval [CI]: 0.93–1.67). Despite not being statistically significant, this result was judged by the Society of Critical Care Medicine (SCCM) to be underpowered[10] and clinically important enough to influence guideline recommendations.

As a result, guidelines from the SCCM[10] and the American Geriatrics Society[11] recommend minimising the use of benzodiazepines in the critically ill and older adult populations. However, intraoperative administration of benzodiazepines during cardiac surgery remains common[12] because of their favourable haemodynamic profile and amnestic properties that are thought to prevent intraoperative awareness. No RCT evidence is available pertaining to the effects of intraoperative benzodiazepine administration. There are two general approaches to intraoperative benzodiazepine administration in current cardiac anaesthesia practice: one which rarely includes benzodiazepines and one which rarely does not include benzodiazepines.[12] There is a need for a trial to evaluate whether broadly implementing an approach to cardiac anaesthesia that rarely includes intraoperative benzodiazepines reduces the incidence of postoperative delirium in adults after cardiac surgery.

To reduce complications and increase efficiency, cardiac surgery is performed in specialized high-volume institutions and is based in large part on the use of institutional standardised procedures, such as preoperative assessment and pre- and postoperative care pathways.[13] Because cardiac care is organised through standard institutional policies, such policies can facilitate evaluating the impact of restricted *vs* liberal intraoperative use of benzodiazepine. Testing the effects of different institutional policies also facilitates a pragmatic trial design, with randomisation of institutions rather than patients, such that the treatment is tested in the setting in which it will be used. Thus, we designed a pragmatic randomised cluster crossover trial to test whether an institutional policy of restricted use of benzodiazepines during surgery (compared with liberal use) reduces postoperative delirium.

To assess the feasibility of this trial, we performed a pilot study (the B-Free Pilot). Our feasibility objectives included assessing the degree of physician adherence to each institutional policy to which the hospital was randomised, and then to the alternate policy to which the hospital crossed over. We also wanted to determine whether measurement of delirium could be achieved using data collected as a part of routine clinical care. Our final goal was to determine the incidence of intraoperative awareness during the restricted benzodiazepine periods.

Methods

Study design

This pilot study was a cluster crossover trial conducted at two sites with four 4 week crossover periods (Fig. 1). An independent statistician created a computer-generated randomisation sequence. Each site was randomised to either the restricted or liberal intraoperative benzodiazepine policy, and then alternated between policies during the remaining three periods. Sites were notified of their initial allocation 1 week before the start of the study.

Study setting and participants

Two Canadian sites participated in the B-Free Pilot. These sites were the Hamilton General Hospital (HGH) in Hamilton, ON, Canada, which provides cardiac surgical care to ~1700 patients annually, and the St Boniface General Hospital (SBGH) in Winnipeg, MB, Canada, which provides cardiac surgical care to ~800 patients annually. Before starting the pilot, it was ensured that all practitioners within each group had clinical equipoise and believed that they could provide cardiac anaesthesia using either policy (i.e. restricted or liberal

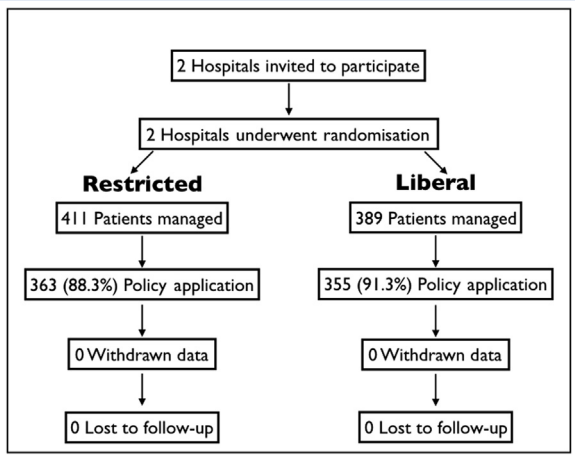

Fig. 1 B-Free Pilot study flow.

intraoperative benzodiazepine). In doing so, we held meetings with each group of cardiac anaesthesiologists, where the rationale for the study and details of the protocol were discussed. Individual anaesthesiologists had the opportunity to ask questions of investigators and to discuss concerns regarding study implementation. Thereafter, in a separate meeting not attended by the study investigators, each cardiac anaesthesiology group reviewed the trial protocol and made a group decision to participate.

Before the start of the trial at each site, we provided information in the form of rounds presentations and e-mails summarising the trial protocol to cardiac surgeons and intensivists practicing in the cardiac surgical ICU. While there was no formal consensus process, investigators at each site spoke personally with members of these stakeholder groups to confirm their support of the trial.

With the exception of intraoperative benzodiazepine administration, which was standardised according to crossover period, all perioperative care of patients undergoing cardiac surgery during the pilot study took place according to standard operating procedures at each site, with no prompts from the study team.

The B-Free Pilot (https://clinicaltrials.gov/ct2/show/NCT03053869) was undertaken from April 3 to July 21, 2017 at the HGH, and from September 18, 2017 to January 7, 2018 at SBGH. All adult patients who underwent cardiac surgery at each site when the study was being conducted were included in the analysis for the period to which the hospital was assigned (restricted or liberal intraoperative benzodiazepine), regardless of their actual treatment. Patients who underwent more than one procedure during the trial were evaluated for their first procedure only.

Patients were provided with a letter before surgery stating that administrative data were being collected as part of an institutional practice evaluation and would be stored anonymously in a database. The letter also contained contact information for research staff, whom they could contact if they wished to withdraw their individual data from the trial. Before starting the trial, we obtained institutional ethics board approval at both sites.

Policies being evaluated

We compared two hospital policies for intraoperative benzodiazepine administration during cardiac anaesthesia. The *restricted benzodiazepine use policy* consisted of no administration of intraoperative benzodiazepines. The *liberal benzodiazepine use policy* consisted of routine administration of intraoperative benzodiazepine. The protocol explicitly allowed exceptions to both policies if there was a strong clinical indication for doing so. Recognised reasons for an exception to the *restricted benzodiazepine use policy* included alcohol withdrawal or benzodiazepine dependence. Recognised reasons for an exception to the *liberal benzodiazepine use policy* included previous adverse reactions to these medications. We anticipated that exceptions to either policy would not occur in more than 20% of patients. We did not specify pre- or postoperative benzodiazepine use, but collected these data.

The pilot feasibility objectives were as follows: (i) to demonstrate that $\geq$80% of patient care would comply with the assigned benzodiazepine administration policy (which was the threshold determined by both cardiac anaesthesia groups to be the minimum proportion of patients who could be managed using either policy, taking into account estimates of the proportion of patients who would require benzodiazepines and for whom benzodiazepines would be clearly contraindicated); (ii) to demonstrate that at least 95% of patients would have at least one delirium assessment completed in the ICU, and that at least 90% of patients would have daily delirium assessments while admitted to the ICU during the study period; and (iii) to demonstrate an incidence of intraoperative awareness of no more than 2% (which represents the upper 95% CI of the pooled incidence of awareness in cardiac surgery patients reported in the literature) during the restricted benzodiazepine period.[14–16] We selected our feasibility threshold for the frequency of delirium assessment because many cardiac surgery patients may have delirium assessed only once per day (despite institutional guidelines mandating assessment every 12 h). This stems from a required level of consciousness ≥ -3 on the Richmond Agitation and Sedation Scale to administer the Confusion Assessment Method for the ICU (CAM-ICU) and the fact that many patients remain in the cardiac surgical ICU for <24 h after operation. We also evaluated the primary and secondary outcomes of the full trial: incidence of delirium in the cardiac surgical ICU, ICU LOS, hospital LOS, and in-hospital mortality.

Delirium assessment

Delirium was assessed in both sites using the CAM-ICU[17] as part of routine practice by nurses in the cardiac surgical ICU. Assessments were conducted at least once every 12 h (i.e. per nursing shift) and with any changes in acuity or mental status.

Blinding

Given the pragmatic nature of our study, which was incorporated into routine clinical care, we elected not to blind cardiac anaesthesiologists to crossover period. Similarly, we did not blind the cardiac surgical ICU nurses who were assessing delirium, as they needed to be able to access all relevant clinical documentation (including anaesthetic records) for patient care. However, we neither informed them that we were conducting a study of intraoperative benzodiazepine administration nor did we communicate the crossover period allocation.

Table 1 Baseline patient characteristics, surgical characteristics, and perioperative benzodiazepine and intraoperative opioid administration by treatment arm. *Single non-CABG procedure includes any single cardiac surgical procedure that did not involve CABG. Examples of this include single valve repair/replacement, isolated aortic repair, and pericardiectomy. †Fisher's exact test was used. ‡Wilcoxon rank-sum test was used. CABG, coronary artery bypass grafting; IQR, inter-quartile range; sd, standard deviation.

	Restricted benzodiazepine use (*n*=411)	Liberal benzodiazepine use (*n*=389)	*P*-value
Patient and surgical characteristics			
Age, mean (SD) (yr)	66.7 (11.3)	67.2 (10.0)	0.484
Male, *n* (%)	317 (77.1)	302 (77.6)	0.864
Urgency of procedure			0.117
Elective, *n* (%)	255 (62.0)	237 (60.9)	—
Urgent, *n* (%)	129 (31.4)	111 (28.5)	—
Emergent, *n* (%)	27 (6.6)	41 (10.5)	—
Type of procedure, *n* (%)			0.531
Isolated CABG*	228 (55.5)	231 (59.4)	—
Single, non-CABG procedure	72 (17.5)	61 (15.7)	—
Two procedures	89 (21.7)	83 (21.3)	—
Three procedures	20 (4.9)	14 (3.6)	—
More than three procedures	2 (0.5)	0 (0.0)	—
Perioperative benzodiazepine administration			
Preoperative benzodiazepines, *n* (%)	61 (14.8)	40 (10.3)	0.056
Postoperative benzodiazepines, *n* (%)	53 (12.9)	40 (10.3)	0.249
Intraoperative benzodiazepines administration, *n* (%)	48 (11.7)	355 (91.3)	<0.0001
Midazolam, *n* (%)	47 (97.9)	348 (98.0)	1.00†
Dose given (mg), mean (SD)	4.6 (2.7)	5.2 (3.5)	0.233
Diazepam, *n* (%)	1 (2.1)	8 (2.3)	1.00†
Dose given (mg), mean (SD)	10.0 (—)	12.5 (4.6)	—
Intraoperative opioid administration			
Intraoperative opioid administration, *n* (%)	411 (100)	388 (99.7)	0.304
Sufentanil, *n* (%)	350 (85.2)	334 (85.96)	0.778
Dose given (μg), mean (SD)	148.1 (80.81)	145.86 (142.4)	0.800
Fentanyl, *n* (%)	65 (165.8)	56 (14.4)	0.576
Dose given (μg), mean (SD)	1108 (637.4)	1245 (588.4)	0.221
Remifentanil, *n* (%)	29 (7.1)	46 (11.82)	0.021
Dose given (μg), mean (SD)	163.2 (93.84)	175.2 (139.640)	0.660
Hydromorphone, *n* (%)	82 (20.0)	78 (20.1)	0.972
Dose given (mg), mean (SD)	1.6 (0.7)	1.8 (2.3)	0.419
Morphine, *n* (%)	2 (0.5)	2 (0.5)	1.00†
Dose given (mg), mean (SD)	7.5 (3.5)	5.0 (0.0)	1.00‡
Total dose given in fentanyl equivalents (μg), median (IQR)	1300 (870.0–2000)	1250 (750.0–2000)	0.432‡

Study data collection

Study personnel extracted intraoperative drug administration from patient charts. All other data were obtained from electronic medical records in Hamilton and from a clinical registry in Winnipeg. We assessed for intraoperative awareness at one site (HGH) by individual patient interview using serial administration of the Brice questionnaire[18] (Supplementary material 1).

Sample size

We sought to demonstrate our ability to successfully implement and crossover between the two benzodiazepine policies, and demonstrate an acceptable difference in benzodiazepine use between study arms. As such, we decided to implement the trial for four 4 week crossover periods, which would require practitioners to crossover three times between four treatment periods (such that each institutional policy would be used twice at each site).

Statistical analyses

For crude comparisons of the characteristics of the pilot population at each site and across policies, we compared proportions using Pearson's χ^2 test or Fisher's exact test and continuous variables using two-sample *t*-test or Wilcoxon rank-sum test as appropriate. We evaluated the feasibility outcomes of this pilot study using descriptive statistics.

Results

During the study periods, 800 patients (540 at HGH; 260 at SBGH) underwent cardiac surgery in the two centres, 411 during the restricted benzodiazepine periods and 389 during the liberal benzodiazepine periods. No patient requested to withdraw their data from the study; we included all patients in our analyses. Table 1 describes the patient characteristics, surgical characteristics, and perioperative benzodiazepine and intraoperative opioid administration by intervention arm. There were no differences between arms in terms of patient age, sex, urgency of procedure, or type of procedure. Amongst all participants, the mean age was 67.0 yr and 77.4% were males. The majority of patients (61.5%) underwent elective cardiac surgical procedures; 30.0% underwent urgent cardiac surgical procedures (performed while the patient was admitted to hospital as an inpatient), and 8.5% underwent emergent cardiac surgical procedures (required within ≤8 h). The most common procedure performed was isolated *coronary*

Table 2 Feasibility outcomes and clinical outcomes of main B-Free trial by intervention arm. CVICU, cardiovascular ICU; IQR, interquartile range; LOS, length of stay. *Managed during limited benzodiazepine period, but received benzodiazepine. †Fisher's exact test was used. ‡Wilcoxon rank-sum test was used.

	Restricted benzodiazepine use (*n*=411)	Liberal benzodiazepine use (*n*=389)	*P*-value
Feasibility outcomes			
Proportion of patients managed according to policy, *n* (%)	363 (88.3)	355 (91.3)	0.171
Proportion of patients with at least one delirium scale assessment in the cardiovascular ICU, *n* (%)	398 (96.87)	372 (95.6)	0.369
Proportion of patients with at least one delirium scale assessment per day in the cardiovascular ICU, *n* (%)	382 (92.93)	358 (92.0)	0.624
Incidence of intraoperative awareness, *n* (%)	1 (0.4%)* (*n*=263)	0 (0) (*n*=258)	1.00†
Outcomes of main trial			
Delirium, *n* (%)	72 (17.5)	55 (14.1)	0.191
ICU LOS (h), median (IQR)	24 (24–48)	24 (24–72)	0.148‡
Hospital LOS (days), median (IQR)	7 (5–11)	7 (5–11)	0.393‡
In-hospital mortality, *n* (%)	5 (1.2)	4 (1.0)	0.801

artery bypass grafting (CABG) (57.4%), followed by cardiac surgery that included two procedures (e.g. CABG and single valve replacement; 21.5%), single, non-CABG procedures (e.g. single valve replacement; 16.6%), and three procedures (e.g. double valve replacement and CABG; 4.3%). Only two patients (0.3%) underwent cardiac surgery that involved more than three procedures.

There were no differences between arms with respect to pre- and postoperative benzodiazepine administration, with 12.6% of patients receiving benzodiazepines before cardiac surgery and 11.6% of patients receiving benzodiazepines after cardiac surgery. Consistent with each policy, 11.7% of patients received intraoperative benzodiazepines during the restricted benzodiazepine periods and 91.3% of patients received intraoperative benzodiazepines during the liberal benzodiazepine periods. We did not document reasons that each policy was not applied, but did informally discuss this with clinical anaesthesia staff. These anecdotal discussions suggested that predictors of patients receiving benzodiazepines during restricted periods included patient history of alcohol/drug use and haemodynamic instability/emergency case status, and that predictors of patients not receiving benzodiazepines during liberal periods included extreme old age/frailty and history of adverse reaction to benzodiazepines.

When intraoperative benzodiazepines were given, midazolam was used in the majority of cases. The mean (standard deviation [SD]) dose of midazolam was 5.1 (3.4) mg when midazolam was administered, although 117/389 (30.1%) of patients who received midazolam in the liberal periods received a dose that equal to or less than 2 mg. There was no difference between the restricted and liberal benzodiazepine periods with respect to the total dose of opioid in fentanyl equivalents, with a median (inter-quartile range [IQR]) dose of 1300 (870–2000) μg given during the restricted benzodiazepine periods and a mean (SD) dose of 1250 (760–2000) μg given during the liberal benzodiazepine periods; *P*=0.848. Supplementary material 2 presents the patient characteristics, surgical characteristics, and delirium scale completion organised by site.

Figure 1 provides an overview of the pilot study flow and protocol adherence. Table 2 describes the primary feasibility and main trial outcomes by intervention arm. There was a higher rate of adherence during the liberal benzodiazepine periods (*P*=0.04), with 365 of 411 patients (88.8%) who underwent surgery during the restricted benzodiazepine periods managed according to the assigned policy, and 362 of 389 patients (93.1%) who underwent surgery during liberal benzodiazepine periods managed according to the assigned policy (Fig. 1; Table 2). There was no difference in delirium scale completion between intervention arms. Overall, a minimum of one nurse-administered delirium scale was collected for 770 of participants (96.3%) during their ICU admission, and 740 participants (92.5%) had at least one nurse-administered delirium scale measurement per 24 h in the ICU. The frequency of delirium scale completion did not differ significantly between sites (see Supplementary material 1).

At one site (HGH), we evaluated 521 of 540 enrolled patients (96.5%) for intraoperative awareness, 263 of 274 participants (96.0%) during the restricted benzodiazepine periods, and 258 of 266 participants (97.0%) during the liberal benzodiazepine periods. The remaining patients were not screened because of intraoperative death, transfer to another hospital or death before extubation, or communication barrier. Four possible cases of awareness were flagged and forwarded for adjudication: two during the restricted benzodiazepine periods and two during the liberal benzodiazepine periods. Of these four cases, one of 521 participants (0.2%), who was managed during a restricted benzodiazepine period, was adjudicated as having intraoperative awareness. Despite being managed during a 'restricted benzodiazepine' period, this patient received an intraoperative benzodiazepine.

There were no differences between intervention arms with respect to the clinical outcomes, including delirium in the cardiovascular ICU, ICU LOS, hospital LOS, and in-hospital mortality. The overall incidence of delirium is 15.9%, with 17.5% of patients experiencing delirium during the restricted benzodiazepine periods and 14.1% of patients experiencing delirium during the liberal benzodiazepine periods (*P*=0.19; RR increase [95% CI] 24.1% [−21.1%, 27.1%]). The median (IQR) ICU LOS was 24 (24–72) h, and the median (IQR) hospital LOS was 7 (5–11) days. The overall incidence of in-hospital mortality was 1.1%.

Discussion

The B-Free Pilot trial demonstrates the feasibility of a large cluster crossover trial evaluating restricted *vs* liberal intraoperative benzodiazepine strategies in patients undergoing cardiac surgery. Our results demonstrate these two approaches to care can be implemented using a cluster crossover design, with both policies applied by anaesthesiologists to more than 85% of patients during each treatment period. The high adherence rate to both policies by individual practitioners demonstrates the clinical acceptability of both approaches by credentialed physicians, further supporting the equipoise in practice and the feasibility of a large trial.

Delirium can be assessed in adequate numbers using delirium scales that are administered and documented by nurses caring for patients after cardiac surgery. By ensuring that we are able to collect the outcomes of our main trial in a high proportion of patients using nurse-administered delirium scales, the pilot trial minimises concerns about incomplete outcome ascertainment based on the use of administrative data in the main trial. Obtaining the trial outcomes using administrative data in the main trial will improve trial efficiency. The pragmatic approach to the implementation of the two benzodiazepine policies and data collection will enhance the external validity of the main trial, as the two policies will be evaluated in everyday clinical practice.

Finally, we showed that intraoperative awareness is rare. In doing so, we used a conventionally recognised approach to assessing awareness, including serial administration of the Brice questionnaire and blinded adjudication. Even though we were not powered to definitively establish the absence of a relationship between benzodiazepine administration and prevention of intraoperative awareness, the fact that only one patient (randomised to the restricted benzodiazepine period who actually received a benzodiazepine) experienced intraoperative awareness is reassuring. We believe this finding, in association with the lack of published evidence supporting benzodiazepines as a means of intraoperative awareness prevention, justifies not formally assessing for awareness as part of the full trial.

The perioperative care of cardiac surgery patients is highly protocolised based on evidence supporting best practice. This includes pre- and postoperative care pathways, intraoperative management strategies, and standardised quality metrics, including the incidence of postoperative delirium. These types of standardised operating procedures (SOPs) are common within perioperative and anaesthesia practice.[13,19] This is because patient care driven by SOPs has been shown to improve individual patient and system outcomes,[20–22] as reflected in recently published cardiac Enhanced Recovery After Surgery (ERAS) guidelines.[13] Cardiac surgery ERAS guidelines for best practice provide 22 recommendations for approaches to care before, during, and after cardiac surgery. Of note, these ERAS guidelines do not provide a recommendation either for or against the use of benzodiazepines, which reflects the lack of supporting evidence. Both restricted and liberal approaches to benzodiazepine administration are routinely used in clinical practice,[12] although the approach selected probably has more to do with practitioner preference than patient characteristics. As perioperative cardiac surgical care is typically standardised using centre-level SOPs, we have chosen to evaluate the impact of standardising intraoperative benzodiazepine administration using two alternate institutional policies.

Our pilot trial has several limitations and generates a number of learning points that have informed the design of the main trial. Although we included a large number of patients from two centres, studying two centres does not mean that we will not encounter issues with adherence and outcome data collection in other sites as part of the main trial. Thus, we have decided that we will only include sites in the trial that have had a formal meeting of their cardiac anaesthesia providers, where the trial and policies are fully explained and discussed amongst the group. After the meeting, cardiac anaesthesia groups will discuss amongst themselves, and will only be included in the trial if 95% of providers commit to following both policies. We are confident that this, in combination with the communication strategies refined during our pilot trial, will ensure high adherence during the main trial.

In keeping with our pragmatic approach, we did not control for pre- or postoperative benzodiazepine administration, nor did we stipulate a minimum benzodiazepine dose for the liberal benzodiazepine policy. However, 13.9% of patients received benzodiazepines before surgery, 11.6% of patients received benzodiazepines after surgery, and 30.1% of patients managed under the liberal benzodiazepine policy received a dose of midazolam of 2 mg or less. To minimise confounding in the main trial, we required that, in the absence of patient-driven reasons (e.g. benzodiazepine dependence, alcohol withdrawal, and seizure), pre- and postoperative benzodiazepines are not administered throughout the duration of the trial, in keeping with current practice guidelines. To ensure an adequate difference in benzodiazepine administration between intervention arms, in the main trial we have stipulated a minimum dose in the liberal benzodiazepine arm of 0.03 mg kg^{-1} ideal body weight midazolam equivalent.

A key challenge in studying delirium using a pragmatic approach is variability between institutions and individuals in the rigour and accuracy with which delirium is assessed. During the pilot study, we did not conduct any formal quality assurance, although the incidence that we identified in each site was aligned with locally reported delirium rates. Recognising the variability in the fidelity with which delirium is assessed, we have taken a number of steps to address this in the main trial. Foremost of these are the appointment of Michael Avidan (Washington University, St Louis, MO, USA) to the trial Steering Committee as the scientific advisor for the assessment of delirium. We will utilise a strategy to optimise the assessment of delirium developed by him. To participate in the main trial, each site must, as part of their standard practice, provide nurses working in the cardiac surgical ICU with formal delirium assessment training and mandate that cardiac surgery patients be assessed for delirium at least once every 12 h using either the CAM-ICU[17] or the Intensive Care Delirium Screening Checklist (ICDSC)[23] while they are admitted to the cardiac surgical ICU. To supplement the training that site nurses already receive, and to ensure standardisation across centres, Avidan has created educational videos about the importance and appropriate use of both the CAM-ICU and ICDSC in assessing delirium. As part of site initiation activities, all cardiac surgical nurses in each participating centre review an educational package that includes these videos. Finally, while we have taken significant efforts to ensure that all participating centres assess delirium with similar rigour, we recognise that there may be variability across centres and individuals with respect to how accurately delirium is assessed. These differences, reflected in part as

variability across centres in the incidence of delirium, are accounted for statistically by the intra-cluster correlation (ICC), which was used in the calculation of our sample size requirement.

Our pilot study was not powered to adequately assess the main trial's primary outcome of delirium. However, the fact that the observed direction of effect was opposite from that anticipated led us to recognise the importance of collecting data about the intraoperative anaesthetic medications administered in the absence of benzodiazepines. We did not identify a difference in opioid administration between arms in the pilot study. However, we did not collect, and thus could not explore, the impact of alternate agents, including propofol, ketamine, and etomidate. Thus, we will collect data regarding all intraoperative medications within in the main trial.

Based on the success of the pilot study, we have established the feasibility of the definitive trial, which will begin in early 2020. There are several unique considerations in determining the sample size requirement for a cluster-randomised trial, including the ICC coefficient, which accounts for the relatedness of clustered data, and the inter-period correlation (IPC) coefficient, which accounts for the temporal nature of patient-important health outcomes at the level of a cluster. The full trial will include 16 hospitals, with an overall average annual case volume of 1000 cardiac surgeries per hospital. Hospitals will be randomised to complete 12 crossover periods of 4 weeks. This design will give us 80% power to detect an RR reduction of 15% in the incidence delirium during the restricted benzodiazepine policy periods based on an assumed incidence of delirium of 15% in the liberal benzodiazepine periods, a conservative ICC of 0.02 based on values determined using several large administrative data sets,[24] and an IPC=0.5*ICC. Sites will be randomised to 12 crossover periods of 4 weeks, blocking in periods of two to minimise period effects.

Finally, there are ethical considerations that are unique to cluster randomised trials, particularly those examining questions related to clinical effectiveness. Individual patient efficacy trials are useful to establish the clinical efficacy of an intervention amongst a carefully selected population under optimal conditions following detailed protocols. However, such trials do not address questions of clinical effectiveness, which are questions about how well an intervention or policy actually works in clinical practice. The question that we are asking within the B-Free trial is a question about the clinical effectiveness of a general approach to care applied at the level of an institution. Thus, in this cluster crossover trial, we are randomising hospitals (i.e. clusters), rather than individual patients. It is not possible to answer a question about the impact of an intervention at the level of a hospital (i.e. cluster) without alterations to individual patient consent.

The Tri-Council Policy Statement (TCPS 2) and US Food and Drug Administration[25,26] have established requirements to justify a waiver of or modification to individual patient consent: (i) altered consent is required to answer the research question, (ii) the research involves minimal risk, (iii) lack of *a priori* consent will not adversely affect participant welfare, (iv) information about the research being conducted is provided to participants when possible, and (v) benefits of undertaking the research outweigh the risks of not obtaining *a priori* consent.

The research question evaluated within the context of the B-Free trial both requires cluster randomisation and satisfies the criteria for waiver of individual consent. We are asking what happens to hospital delirium incidence when an institutional policy of one therapeutic strategy is compared with another. This question can only be answered by randomising at the institutional level, as in a cluster crossover trial. Many factors may impact effectiveness beyond the efficacy of the policy itself. Specifically, issues around practitioner adherence to the policy (reflecting knowledge translation) or policy application at the level of the individual patient (reflecting population selection) are not accounted for in individual participant randomised trials, but are captured by cluster trials utilising alterations to individual patient consent. B-Free evaluates two different cardiac anaesthesia policies related to the use of benzodiazepines (restricted *vs* liberal intraoperative administration), both of which are used by credentialed anaesthesiologists in routine practice.[12] Whether a patient undergoing cardiac surgery receives or does not receive benzodiazepines is largely determined by practitioner preference, rather than patient considerations. To satisfy the criteria for minimal risk, patients exposed to both intervention and control arms must experience no more risk than they would in routine practice. Given that both approaches to benzodiazepine administration are currently used in routine practice, this satisfies the criteria for minimal risk.

Given that patients do not routinely consent to their anaesthetic (as consent to anaesthesia is implied with consent to surgery), we do not believe that the lack of *a priori* consent will adversely affect patient welfare, as both benzodiazepine approaches are routinely used, exceptions are allowed when clinically indicated, and only anonymised data are being collected. Within the trial, we notify patients (through provision of a letter of information) that the hospital, in which they are undergoing cardiac surgery is currently studying alternate institutional policies with respect to the medications that comprise their cardiac anaesthetic. Within the letter, patients are informed of the two policies and notified that, if their anaesthesiologist believes that there is a clinical reason that would make policy application unsafe in their individual case, the policy will not be applied. Patients are also notified that anonymised data are being collected as part of the study (although they will not be contacted by research staff) and that, if they object to this, they may request to have their personal information withdrawn from the trial database. Finally, establishing the optimal approach to intraoperative benzodiazepine use is important to guide cardiac anaesthesia practice. The information obtained has the potential to benefit both patients and society by reducing delirium and its associated morbidity in patients undergoing cardiac surgery, thus satisfying the final requirement for alterations to individual patient consent.

Conclusions

Delirium continues to occur in 15–20% of patients in the ICU after cardiac surgery. It is associated with significant morbidity and mortality, and may be attributable to the ongoing use of benzodiazepines during surgery. Alternatives to benzodiazepines exist, and there is now uncertainty as to whether or not benzodiazepines should be used during surgery, as shown by the large variation in clinical practice in Canada. This heterogeneity in practice reflects the lack of evidence.

There is a need for a trial to determine the optimal approach to benzodiazepine (restricted *vs* liberal) administration during cardiac surgery. In the B-Free pilot trial, we have demonstrated the feasibility of a multicentre cluster crossover

trial addressing this important question. We have demonstrated that we can achieve widespread adherence to both intervention arm policies, collect the primary outcomes of the main trial using only delirium assessments collected as part of routine clinical care, and that a restricted intraoperative benzodiazepine approach is not associated with an increased risk of intraoperative awareness.

Authors' contributions

Study conception/design: JS, EB-C, EJ, SFL, RW, SB, SS, RA, AL, SC, PJD
Data acquisition: JS, EB-C, SS, AS, SM, AL, SL, KU, WM, MK, IF, RA
Data analysis/interpretation: JS, EB-C, EJ, SFL, RW, SB, SC, PJD
Drafting of final manuscript: JS, EB-C, EJ, SFL, RW, SB, SS, WM, AL, SC, PJD
All authors have reviewed and approved the final manuscript submitted for publication, and agree to be accountable for all aspects of the work

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Declarations of interest

PJD is a member of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums or payments from industry to support research endeavours and costs to participate in meetings. Based on study questions PJD has originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics, Siemens, and Stryker. PJD has participated in advisory board meetings for GlaxoSmithKline and Boehringer Ingelheim. He also attended an expert panel meeting with AstraZeneca and Boehringer Ingelheim. No other competing interests are declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.03.030.

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