Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"

The GUARDIAN Pilot Trial

Single-center prospective randomized pilot trial

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Summary

We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

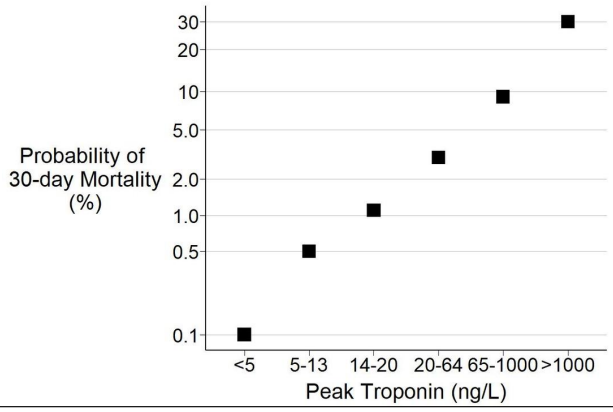
In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol. The pilot trial of 80 cases will be designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control *versus* routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day *versus* immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Introduction

When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is 1,000 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3] Most postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The two most common and comparable causes of 30-day mortality after non-cardiac surgery are major bleeding which cannot easily be prevented, and myocardial injury which possibly can be; sepsis is a distant third.[4]

Myocardial injury after non-cardiac surgery (MINS) is defined by troponin elevation of presumably ischemic origin, and is highly associated with 30-day[5] (Fig. 1) and one-year[6] mortality. Myocardial infarction (MI), per 4th Universal Definition, is defined by troponin elevation *and* either symptoms or signs of myocardial ischemia.[7] More than 90% of MINS and MI occur within the initial two postoperative days.[8] Both are strongly associated with many *unmodifiable* baseline characteristics including age, diabetes, and cardiovascular history. In large randomized trials (n=7,000-10,000), we have shown that MI cannot be safely prevented by beta blockers,[9] avoiding nitrous oxide,[10] clonidine,[11] or aspirin.[12] In a recent large trial, one patient in seven who had MINS suffered re-infarction within 17 postoperative months.[13]

Fig. 1. 30-day mortality as a function of postoperative peak high-sensitivity troponin T. Mortality increases markedly from 0.1% at a troponin T concentration <5 ng/L to 30% mortality when troponin T exceeds 1,000 ng/L. Data from The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between complications and death within 30 days after noncardiac surgery. Can Med Assoc J 2019; 191: E830-E7



Intraoperative hypotension is associated with MINS and MI, with the harm threshold being a mean arterial pressure (MAP) ≈65 mmHg (Fig. 2).[14,15] The harm threshold for acute kidney injury (AKI) is similar,[14,16,17] and 40% of Stage 2 AKI persists or is worse 1-2 years after surgery (Turan, Anesthesiology, in press). We and others have also shown that postoperative hypotension is associated with myocardial infarction, *independent of intraoperative hypotension* (Fig. 3).[18,19]

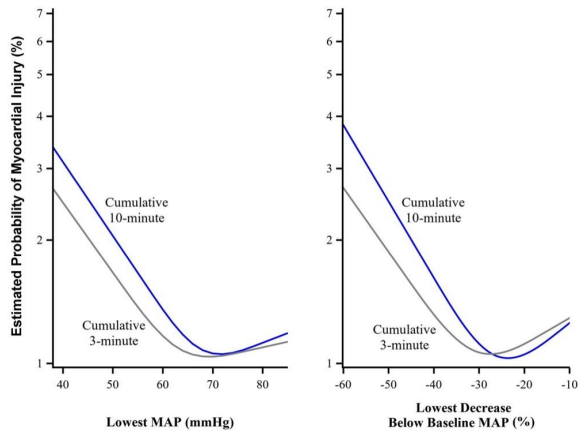


Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after non-cardiac surgery. The left graph shows the relationship between the lowest cumulative absolute mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. The right graph shows the relationship between the lowest cumulative relative mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. Both graphs are multivariable logistic regressions adjusted for baseline characteristics and smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. From Salmasi, et al: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after non-cardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126: 47-65.

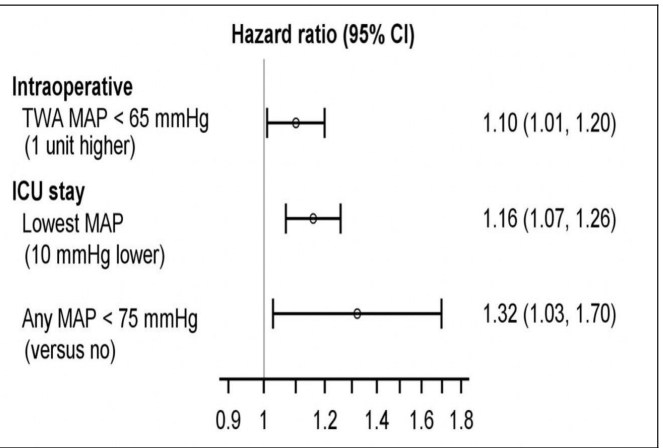


Fig. 3. Odds ratios of average relative effect on the primary composite of 30-day myocardial infarction and mortality for three perioperative periods: intraoperative, remaining day of surgery, and the initial four PODs of hospitalization. CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, P < 0.017 (0.05/3) was considered to be significant for the average relative effect. The circles present the odds ratios, and the bars present the CIs. POD = postoperative day. From Sessler et al: Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: A substudy of the POISE-2 trial. Anesthesiology 2018; 128: 317-27

There is currently sparse evidence that the associations are casual. But a small fragile randomized trial (n=292) shows that preventing intraoperative hypotension reduces the risk of major complications by 25%.[20] Perioperative hypotension is also associated with stroke,[9,21-24] although inconsistently.[25] Blood pressure — specifically hypotension prevention — is therefore a modifiable factor that may reduce cardiovascular complications.

Delirium is a common complication of cardiac surgery and is associated with morbidity and mortality.[26-32] The reported incidence of delirium after major non-cardiac surgery is typically about 10%, and increases markedly as age increases beyond 65 years. The pathophysiology of delirium is multifactorial but surely includes inadequate brain perfusion that results when mean arterial pressure is less than the lower limit of autoregulation.[33-35] Consistent with this theory, hypotension is associated with delirium and cognitive decline,[28,36,37] although inconsistently.[27,38,39] Limited randomized data (n=199) indicate that hypotension causes delirium.[40] Patients who have delirium after surgery are far more likely than others to develop long-term cognitive impairment,[41] although it remains unknown whether the association is causal. Hypotension may also provoke overt or (far more commonly) covert strokes which is strongly linked to delirium.[42]

No robust randomized trial has been published.

Specific Aims

Mortality in the 30 days after surgery is surprisingly common, and usually occurs during the initial hospitalization. Major bleeding and cardiovascular complications are the most common causes of 30-day postoperative mortality. Cardiovascular complications are independently associated with intraoperative and postoperative hypotension. Cognitive impairment, both acute delirium and long-term, are common after major surgery. There is increasing evidence that perioperative hypotension may contribute to brain injury. However, there is currently only sparse and fragile randomized evidence indicating that intraoperative hypotension prevention reduces cardiovascular risk and/or cognitive impairment in non-cardiac surgical patients. We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

Aims

First, we will test whether there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected).

Second, that restarting routine antihypertensive medications per protocol should be feasible (restart delayed until the third postoperative day versus immediate restart).

We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Methods

The trial will be conducted with IRB approval and written patient consent will be obtained. There will be no restriction on sex, or ethnicity. All qualifying patients will be asked to consider the trial. The trial is restricted to patients ≥45 years old because cardiovascular outcomes are rare in younger patients, but there is no upper age restriction. The trial will be registered on ClinicalTrial.gov before enrollment.Pilot patients will be enrolled before normal enrollment.A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines.

Subject selection

Consenting patients will be **eligible** if they are:

1. Scheduled for major noncardiac surgery expected to last at least 2 hours;
2. Having general endotracheal anesthesia;
3. Expected to require at least overnight hospitalization;
4. Are designated ASA physical status 2-4;
5. Chronically taking at least one anti-hypertensive medication;
6. Expected to have direct blood pressure monitoring with an arterial catheter;
7. At least 45 years old;
8. Cared for by clinicians willing to follow the protocol;
9. Subject to at least one of the following risk factors:
    a. History of peripheral arterial surgery;
    b. History of coronary artery disease;
    c. History of stroke or transient ischemic attack;
    d. Serum creatinine >175 μmal/L (>2.0 mg/dl);
    e. Diabetes requiring medication;
    f. Current smoking or 15 pack-year history of smoking tobacco
    g. Scheduled for major vascular surgery
    h. Body mass index ≥35 kg/m^2;
    i. Preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent
    j. B-type natriuretic protein (BNP) >80 ng/ml or N-terminal B-type natriuretic protein (NT-ProBNP) >200 ng/ml.

Patients will be **ineligible** if they:

1. Are scheduled for carotid artery surgery;
2. Are scheduled for intracranial surgery;
3. Are scheduled for partial or complete nephrectomy
4. Are scheduled for pheochromocytoma surgery;
5. Are scheduled for liver transplantation;
6. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension or relatively high pressure required for carotid artery surgery;
7. Have end-stage renal disease requiring dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min;
8. Have a documented history of dementia;
9. Have language, vision, or hearing impairments that may compromise cognitive assessments;

Protocol

Consenting patients who take either ACEIs or ARBs will be asked not to take the medications on the morning of surgery, and instead bring them with them to the hospital. Qualifying patients will be randomly allocated using computer-generated assignments 1:1 ratio without stratification in a block of four. Allocation will be concealed within sealed opaque envelopes until shortly before anesthesia induction. Allocation will thus remain concealed until the last practical moment. Randomization will be implemented by clinicians in collaboration with research personnel. Arterial catheter transducers will be positioned at the level of the right atrium, and adjusted as necessary if

patient position is changed. A fast-flush square-wave test will be performed shortly after catheter insertion to confirm that dynamic characteristics of the pressure monitoring system are appropriate.[10]

The treatments will be:1) norepinephrine infusion to maintain intraoperative MAP ≥85 mmHg, delayed resumption of chronic antihypertensive medications, and a target ward systolic pressure of at least 120 mmHg (tight pressure management); or, 2) routine intraoperative blood pressure management and prompt resumption of chronic antihypertensive medications (routine pressure management)

Tight pressure management: In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) will not be given the morning of surgery. Clinicians will be encouraged to insert the required arterial catheter before anesthetic induction because much hypotension occurs shortly after anesthetic induction.[46] A norepinephrine infusion (in the preferred local concentration) will be prepared, connected to an intravenous catheter, and activated at a low rate. Norepinephrine can be safely given through a central catheter or peripherally. In a recent study of 14,328 patients, there were only 5 extravasation events and not a single patient experienced local tissue injury.[47] It can be substituted if norepinephrine is contraindicated or impractical.

General anesthesia will be induced with propofol which will be given in repeated small boluses in an effort to keep intraoperative MAP ≥85 mmHg. Simultaneously, the vasopressor infusion will be adjusted with the same goal. Anesthetic dose, fluid administration, and vasopressor administration will be adjusted with the goal of maintaining intraoperative MAP ≥85 mmHg.

Resumption of chronic anti-hypertensive medications will be delayed until the third postoperative day unless deemed necessary to treat hypertension or for some other clear indication (e.g., preventing atrial fibrillation in a chronic beta-blocker user) because >90% of MINS occurs within 48 hours after surgery. When necessary to treat hypertension, chronic antihypertensive or new medications can be used per clinician preference. Clinicians will make what efforts they can to maintain postoperative systolic pressure of at least 120 mmHg during the initial three postoperative days by maintaining adequate hydration, using inotropic and chronotropic drugs, and vasopressor as necessary. This protocol specifies the blood pressure target, but leaves implementation to clinical judgement.

Routine pressure management: In patients assigned to routine pressure management, ACEIs and ARBs can be given the morning of surgery if deemed appropriate by the attending anesthesiologist. The arterial catheter will be inserted before or after induction of anesthesia per clinician preference. General anesthesia will be induced and maintained per routine. Intraoperative pressure management will be per routine. As usual, chronic anti-hypertensive medications will be restarted shortly after surgery unless contraindicated by hypotension.

In both groups, other aspects of anesthetic management will be at the discretion of the responsible anesthesiologist, including the types and volumes of various fluids. Volatile or intravenous anesthesia is permitted. There is increasing evidence that deep anesthesia promotes delirium and long-term cognitive dysfunction (Evered, in review).[49] Therefore, processed EEG monitoring, such as the Bispectral Index (BIS) or Patient State Index (PSI), should be used. If BIS is

the method, a value of 50 should be targeted from soon after induction until shortly before emergence. If another EEG system is used, a comparable hypnotic depth should be targeted.

There will be no limitation on ancillary vasoactive, chronotropic, and inotropic drugs. Clinicians will be free to use advanced hemodynamic monitoring (e.g., FlowTrac, esophageal Doppler, etc.). Blood products will be given per routine. Similarly, postoperative analgesic management will be per routine and clinician preference. Neuraxial and peripheral nerve blocks are permitted, but epidural catheters should not be activated until surgery is nearly finished.

Because patients must be fairly sick to qualify for Pilot GUARDIAN, some will go to directly from surgery to critical care units, or much less often, become unstable and require transfer from a routine ward to an ICU. In either case, every effort will be to maintain randomized treatments and blood pressure targets.

In all cases, good judgement will predominate. Clinicians should always act in their patients' best interests, irrespective of the GUARDIAN protocol.

Measurements

Baseline

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Routine anesthetic variables will be recorded including volatile anesthetic partial pressure, Fluid type and volume, estimated blood loss, and transfusions. Cardiovascular risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular medications will be similarly recorded by category, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. Types of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), thoracic, urologic, gynecologic, vascular, and other. Timing will be characterized as elective, urgent, or emergent.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, and NT-ProBNP. Baseline electrocardiogram and echocardiogram interpretations will also be recorded as available, as will hemoglobin and creatinine other than specified below.

Perioperative

Blood pressure is our primary exposure and will therefore be carefully recorded. The most recent pressure from a clinic assessment will be used. Our institution have electronic anesthesia records that will automatically record systolic, mean, and diastolic pressures from the required arterial catheter at no less than 1-minute intervals. When possible, we will obtain electronic data which are efficient, denser, and more reliable than manual recording. But where necessary, intraoperative blood pressures will be recorded manually at 5-minute intervals. Ward blood pressure will normally be recorded by nurses at 8-hour-intervals. Any pressures obtained for clinical purposes will be recorded for use in the trial.Additional ward pressures might also be obtained. However, all blood pressures during the initial three postoperative days will be retrieved and included in the trial database. We will restrict recording to this period because >90% of postoperative myocardial injury occurs within the

initial two postoperative days. High-risk patients may require ICU admission. Blood pressure is measured frequently in critical care units, and all available pressures will be recorded.

We will require **creatinine** preoperatively (within 30 days), and on the initial three postoperative days while patients remain hospitalized. Additional values obtained for clinical reasons will be recorded during the initial 30 postoperative days. Hemoglobin will be recorded on an as-available basis for the initial three postoperative days.

Blood for generations 4 or 5 **troponin** T, or troponin I will be recorded preoperatively up to 30 days before surgery, and on the first three postoperative days so long as patients remain hospitalized.[8] Additional troponin samples will also be obtained if patients have shortness of breath or experience chest, neck, or arm pain. Blood troponin concentrations exceeding thresholds (depending on individual types of troponin tests) should prompt cardiology consultation, an electrocardiogram, and when practical an echocardiogram.

Myocardial injury will be diagnosed by objective screening based on preoperative and first three postoperative day troponin I values crossing specific thresholds for MINS so long as patients remain hospitalized. Abnormal troponin concentrations will be evaluated as clinically indicated with ECG, echocardiography, and clinical symptoms; the resulting values will be recorded, as will other cardiovascular interventions such as angioplasty. MINS will be diagnosed by troponin exceeding thresholds apparently of ischemic origin (e.g., no other obvious cause for artifactual elevation). Myocardial infarction will also be centrally adjudicated and require *both* MINS and at least one symptom (e.g., chest pain or shortness of breath) or sign (e.g. ECG or echocardiogram abnormality).

We will consider all patients who had an elevated serum troponin concentration anytime during the first 30 days after surgery and determine the presence of any ischemic features (*i.e.*, whether patients fulfilled the universal definition of myocardial infarction),[50] whether there was a non-ischemic etiology that could explain the elevated troponin measurement, and whether the myocardial injury appears to have occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event).

Myocardial injury after non-cardiac surgery will be defined as having values exceeding local 99th percentile for troponin I. Patients meeting diagnostic criteria for MINS will be evaluated for myocardial infarction with an electrocardiogram, echocardiogram (when possible), and a cardiac consultation. Non-fatal cardiac arrest and mortality will be determined from case-reports and medical records. Strokes will be detected based on clinical symptoms, and require radiographic evidence consistent with new-onset cerebral ischemic or hemorrhagic injury.

Delirium will be assessed 7-10 AM and 5-8 PM for the initial four postoperative days while patients remain hospitalized because this approach will detect nearly all postoperative delirium (Fig. 4). Delirium will not be evaluated the evening after surgery because confusion might result from residual anesthetic effects. We will use the 3D-CAM which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[51] The test works well in patients with dementia.[51] CAM-ICU, which is also well validated, will be substituted when patients are intubated.[52] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will analyzed dichotomously.

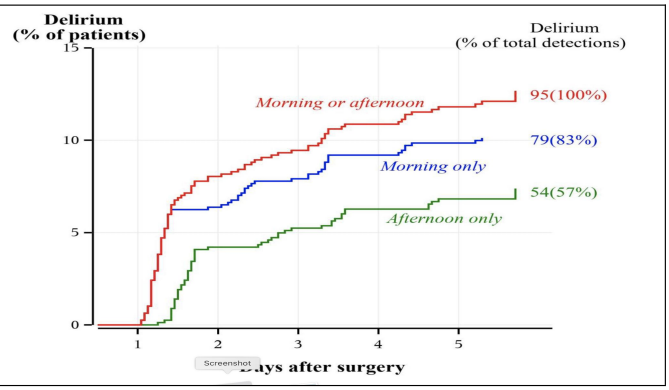


Fig. 4. Detection of delirium with CAM-ICU as a function of assessment times over postoperative days 1-5. Nearly all delirium was detected with twice daily assessments for the initial four postoperative days. From Hamadnalla, et al, in review.

Acute kidney injury. Postoperative Acute Kidney Injury will be defined by Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines.110 By convention in perioperative studies, urine output will not be considered since it is rarely available.111 Specifically, patients will be considered to have Stage 1 acute kidney injury (risk) if the postoperative serum creatinine increases at 1.5-1.9-fold or by more than 0.3 mg/dl (≥26.5 μmol/L) within a 48-hour period. Stage 2 will be defined by a 2.0-2.9-fold increase in creatinine, and Stage 3 will be defined by a 3-fold increase in creatinine or an increase from baseline by ≥4 mg/dl (≥353.6 μmol/L) or initiation of renal replacement therapy.We will compare the preoperative creatinine concentration closest to surgery to the highest postoperative concentration measured within 7 days. Only Stages 2 and 3 will be considered for the primary perioperative composite.

Outcomes and clinically meaningful differences

The first co-primary feasibility outcomes are the fraction of time when intraoperative MAP >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The area of MAP below (above) a threshold refers to the cumulative sum of areas for the MAP-time curve below (above) the specified threshold.

The second co-primary feasibility outcome is postoperative blood pressure management, characterized by the time routine antihypertensive medications restarted after surgery.

The secondary feasibility outcome measures are time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.

The exploratory efficacy outcome measures are: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect; or is a medically important event.

Suspected unexpected serious adverse reactions (SUSARs) are events that meet the following criteria: 1) suspected to be causally associated with blood pressure management, anesthetic induction agent, or vasopressor; 2) unexpected if the nature, severity, or outcome of the reaction(s) is

not consistent with the reference information (i.e., product monograph for trial drugs); 3) serious (as defined above for an SAE); and 4) not a defined efficacy.

Efficacy and safety outcomes will be recorded separately and not as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions), will not be regarded as SAEs. This pertains also to hospitalizations which are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study (e.g., patient returning to the hospital for chemotherapy), and which did not result in a worsening of the disease.

All SAEs need to be reported within 48 hours of knowledge of the event to the Project Office. For such events, research personnel will complete an SAE CRF in the database. The Project Office will then inform regulatory authorities in a timely manner, as necessary, according to the applicable regulations.

The DMC will provide oversight of patients' safety throughout the trial by reviewing aggregate data (including all reported study outcome events and SAEs) by treatment group at regular intervals throughout the duration of the trial and as defined in the DMC Charter.

Data Analysis

Primary, secondary, and exploratory outcomes will be analyzed on a modified intent-to-treat basis by randomized group assignments. Specifically, we will include all randomized patients who have surgery, even if the operation is changed to one that would not otherwise qualify for Pilot GUARDIAN.

Balance on baseline characteristics will be assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups are considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [$1.96*\text{sqrt}(1/n_1 + 1/n_2)$].

We primarily evaluate the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests will be used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

Sample Size Considerations

The study will enroll 40 patients in each treatment group. Design analysis for the study will be done after data collection but before we conducted the analysis.

The fraction of time spent above 85 mmHg is assumed to be distributed as Beta (5, 5) and with the above sample size, the confidence interval half-width for estimating the mean would be 0.05 which is deemed to be sufficiently precise. The beta distribution is appropriate as the outcome is restricted to the closed interval between 0 and 1. The observed confidence interval widths are 0.01.

Schedule of Procedures

	BP	anti-HP medicine	Creatinine	Troponin I+ECG(Positive)	3D-CAM/ICU-CAM	Perfusion-related complications	Mortality
Baseline(<30d)	Y	Y	Y	Y			
DOS	IBP+MAP≥85/IBP	Y/N	Y	Y			
POD1	Y	Y/N	Y	Y	Twice		
POD2	Y	Y/N	Y	Y	Twice		
POD3	Y	Y			Twice		
POD4		Y			Twice		
Ward request	Y	Y	Y	Y			
Discharged						Y	Y
POD30-35						Y	Y

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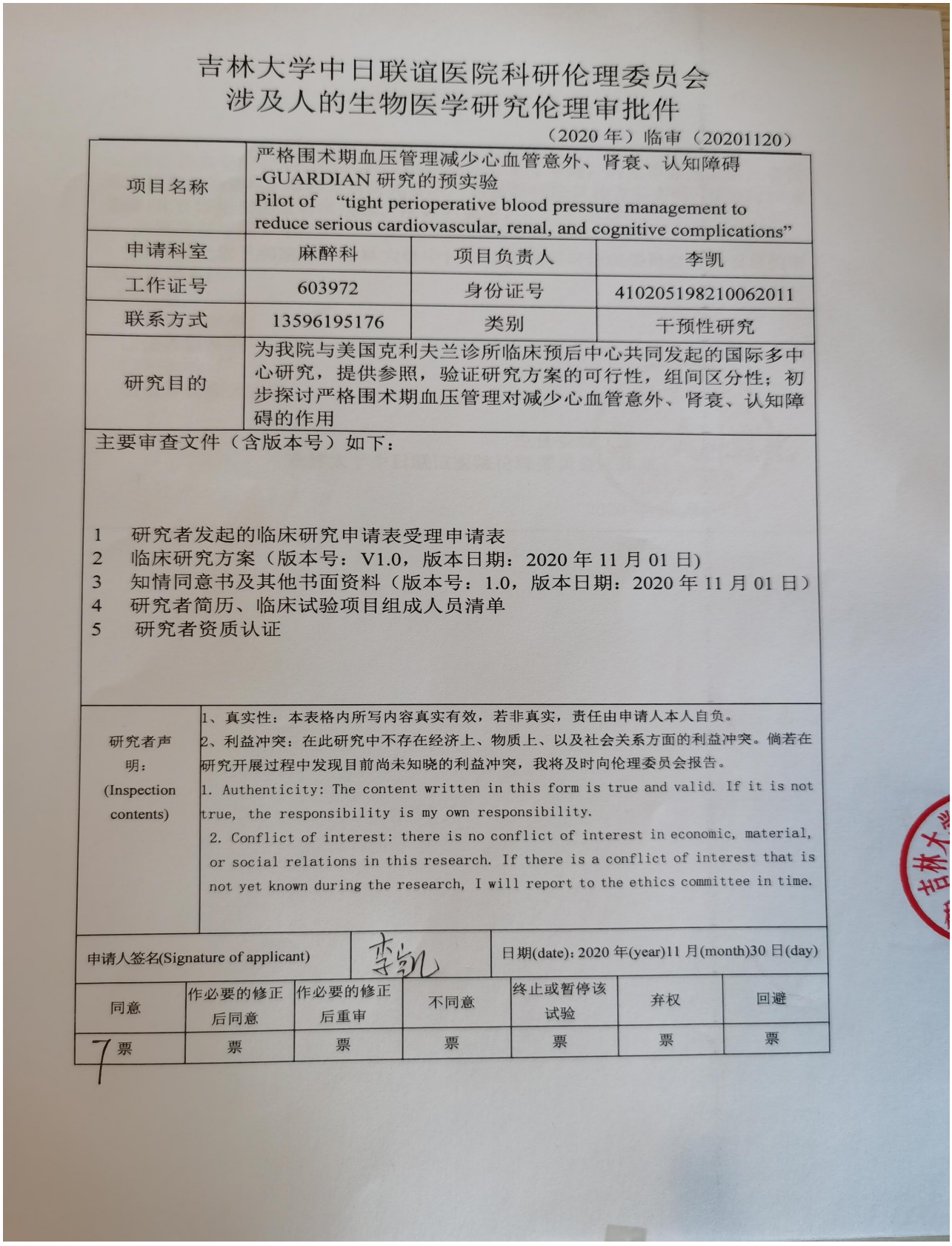

吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

项目名称	严格围术期血压管理减少心血管意外、肾衰、认知障碍-GUARDIAN 研究的预实验 Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"		
申请科室	麻醉科	项目负责人	李凯
工作证号	603972	身份证号	410205198210062011
联系方式	13596195176	类别	干预性研究
研究目的	为我院与美国克利夫兰诊所临床预后中心共同发起的国际多中心研究，提供参照，验证研究方案的可行性，组间区分性；初步探讨严格围术期血压管理对减少心血管意外、肾衰、认知障碍的作用		

主要审查文件（含版本号）如下：

1 研究者发起的临床研究申请表受理申请表
2 临床研究方案（版本号：V1.0，版本日期：2020 年 11 月 01 日）
3 知情同意书及其他书面资料（版本号：1.0，版本日期：2020 年 11 月 01 日）
4 研究者简历、临床试验项目组成人员清单
5 研究者资质认证

研究者声明：(Inspection contents)	1、真实性：本表格内所写内容真实有效，若非真实，责任由申请人本人自负。 2、利益冲突：在此研究中不存在经济上、物质上、以及社会关系方面的利益冲突。倘若在研究开展过程中发现目前尚未知晓的利益冲突，我将及时向伦理委员会报告。 1. Authenticity: The content written in this form is true and valid. If it is not true, the responsibility is my own responsibility. 2. Conflict of interest: there is no conflict of interest in economic, material, or social relations in this research. If there is a conflict of interest that is not yet known during the research, I will report to the ethics committee in time.

申请人签名(Signature of applicant)	李凯	日期(date)：2020 年(year)11 月(month)30 日(day)

同意	作必要的修正后同意	作必要的修正后重审	不同意	终止或暂停该试验	弃权	回避
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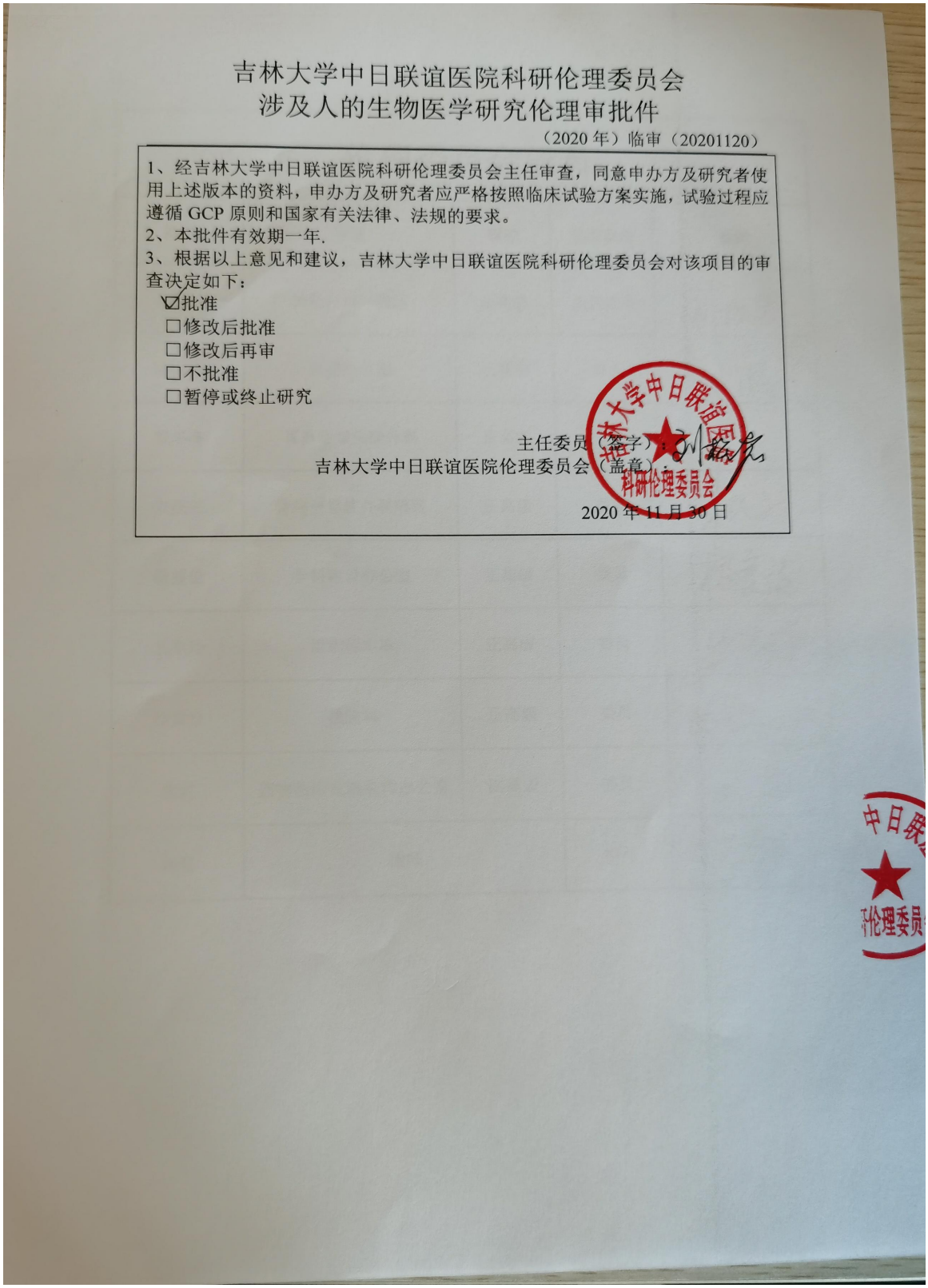

吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

1、经吉林大学中日联谊医院科研伦理委员会主任审查，同意申办方及研究者使用上述版本的资料，申办方及研究者应严格按照临床试验方案实施，试验过程应遵循 GCP 原则和国家有关法律、法规的要求。
2、本批件有效期一年.
3、根据以上意见和建议，吉林大学中日联谊医院科研伦理委员会对该项目的审查决定如下：

☑批准
☐修改后批准
☐修改后再审
☐不批准
☐暂停或终止研究

主任委员（签字）：
吉林大学中日联谊医院伦理委员会（盖章）：
2020 年 11 月 30 日