The Choice of Vasopressor for Treating Hypotension During General Anesthesia: a Pilot Pragmatic Cluster Cross-over Randomized Trial (the VEGA-1 Trial)

NCT04789330

Document Date: October 17, 2022

1.0 General Information

***Enter the full title of your study:**

The choice of vasopressor for treating hypotension during General Anesthesia: a pilot pragmatic cluster cross-over randomized trial (the VEGA-1 trial)

***Enter the study alias:**

VEGA-1 trial
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◆	**UCSF** - *127037* - M_Anesthesia

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Legrand, Matthieu M MD, PhD, MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Agrawal, Ashish
Other Investigator
Bokoch, Michael P, MD PhD
Co-Principal Investigator
Chen, Catherine L, MD, MPH
Other Investigator
Chen, Lee-Lynn
Other Investigator
Fields, Scott M

Other Investigator
Kothari, Rishi P
Other Investigator
Kurien, Philip A, MD
Other Investigator
Lew, Vincent K
Other Investigator
Li, Fanny
Other Investigator
Mavrothalassitis, Orestes
Other Investigator
Niemann, Claus MD, MD
Other Investigator
Palaniappa, Nandini C
Other Investigator
Pirracchio, Romain MD PhD
Other Investigator
Stein, Deborah M
Other Investigator
Whitlock, Elizabeth MD
Other Investigator
Yoo, Susan S
Other Investigator
Yoon, Susan
Other Investigator

B) Research Support Staff

Ansay, Christopher
Volunteer – Not permitted at UCSF; allowed at SF VAHCS
Armstrong, Rachelle L
Data Manager
Bi, Emily
Study Coordinator
Fong, Nicholas B
Research Assistant
Jacobson, Adam Z
Data Manager
Joo, Hyundeok
Clinical Research Associate
Krone, Sina E
Research Assistant
Nguyen, Kevin H
Clinical Research Associate
Reddy, Nikitha P
Study Coordinator
Spinner, Jon D
Data Manager
Sturgess-DaPrato, Jillene
Study Coordinator

3.3 *Please add a Study Contact

Bokoch, Michael P, MD PhD

Legrand, Matthieu M MD, PhD, MD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

Gropper, Michael Allan, MD, PhD

Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated May 2021 - Revised Common Rule (January 2018) Compliant / COVID-19 - v97

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

VEGA-1 is a pragmatic, cluster-randomized, open-label, multiple-crossover pilot clinical trial of two different vasopressors commonly used to treat low blood pressure (hypotension) during major surgery under general anesthesia: norepinephrine (NE) and phenylephrine (PE). Hypotension during general anesthesia is extremely common and may rapidly compromise perfusion of vital organs. Even brief periods of hypotension can precipitate injury to the heart, brain, or kidneys, and worsen postoperative outcomes. Given the millions of patients that undergo surgery worldwide each year, solving this seemingly simple dilemma could have a tremendous impact on global anesthesia practice. We hypothesize that using NE as the primary vasopressor infusion will reduce major adverse events, given that NE has b-agonist effects that raise cardiac output whereas PE does not. Both drugs are standard-of-care, and are readily available and familiar to anesthesia providers. We will implement VEGA-1 at three UCSF hospitals (Parnassus, Mission Bay, Mount Zion), the Zuckerberg San Francisco General Hospital, and UCLA Medical Center. Each hospital will be cluster-randomized such that all eligible patients receive either NE or PE infusions during a given month. Deidentified data will be securely extracted from the electronic medical record in an automated fashion. Successful completion will provide data necessary to design a larger, multi-center trial to definitively test the superiority of one vasopressor over the other.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- (•) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)

- ○ Social, behavioral, educational, and/or public policy research
- ○ Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- ◉ Yes (including phone, email or web contact)
- ○ No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

- ◉ Minimal risk
- ○ Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- ○ Full Committee
- ◉ Expedited
- ○ Exempt

4.7 * EXPEDITED REVIEW CATEGORIES: (REQUIRED) If you think this study qualifies for expedited review, select the regulatory categories that the research falls under: (check all that apply)

- ☑ Category 1: Research using approved drugs or devices being used for their approved indications
- ☐ Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture in certain populations and within certain amounts
- ☐ Category 3: Prospective collection of biological specimens for research purposes by noninvasive means (e.g. buccal swabs, urine, hair and nail clippings, etc.)
- ☐ Category 4: Collection of data through noninvasive, routine clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc. - no sedation, general anesthesia, x-rays or microwaves)
- ☑ Category 5: Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for nonresearch purposes
- ☐ Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes
- ☐ Category 7: Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factorsevaluation, or quality assurance methodologies

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

- ○ Yes ◉ No

4.10 * CLINICAL TRIAL: (REQUIRED)
Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

(•) Yes ( ) No

*** Clinical Trial Registration** - 'NCT' number for this trial: **(REQUIRED)**

NCT04789330

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

- [ ] Phase 0
- [ ] Phase 1
- [ ] Phase 1/2
- [ ] Phase 2
- [ ] Phase 2/3
- [ ] Phase 3
- [x] Phase 4
- [ ] Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CORONAVIRUS RESEARCH: (REQUIRED) Does this study involve research on coronaviruses (COVID-19, SARS, MERS or other):

○ Yes ◉ No

4.15 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

○ Yes ◉ No

4.16 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

○ Yes ◉ No

4.17 * SCIENTIFIC REVIEW: (REQUIRED) If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- ☐ Funding agency, cooperative group, study section or other peer-review process
- ☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- ☐ CTSI Clinical Research Services (CRS) Advisory Committee
- ☐ CTSI Consultation Services
- ☑ Other:
- ☐ Has not undergone scientific/peer review

* Specify entity that provided review: **(REQUIRED)**

Anesthesia and Perioperative care departmental scientific review

4.18 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires IRB and GESCR review
○ Yes, and requires GESCR review, but NOT IRB review

4.19 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

○ Yes ◉ No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

○ Yes ◉ No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

○ Yes ◉ No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	Intl Anesthesia Research Society	05	UCSF	Grant		A135759

Sponsor Name:	Intl Anesthesia Research Society
Sponsor Type:	05
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	A135759
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	The choice of vasopressor for treating hypotension during general anesthesia: a pilot pragmatic cluster cross-over randomized trial (the VEGA-1 trial)
PI Name: (If PI is not the same as identified on the study.)	LEGRAND
Explain Any Significant Discrepancy:	

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- [x] Funded by gift (specify source below)
- [ ] Funded by UCSF or UC-wide program (specify source below)
- [x] Specific departmental funding (specify source below)
- [ ] Unfunded (miscellaneous departmental funding)
- [ ] Unfunded student project

* Identify the gift, program, departmental, or other internal funding source: **(REQUIRED)**

IMPACT grant from the International Anesthesia Research Society (IARS)

6.0

Sites, Programs, Resources, and External IRB Review

6.1 * UCSF AND AFFILIATED SITES (check all that apply): (REQUIRED)

- [ ] UCSF Benioff Children's Hospital Oakland (BCH OAK)
- [ ] UCSF Cancer Center Berkeley
- [ ] UCSF Cancer Center San Mateo
- [ ] UCSF China Basin clinics and facilities
- [ ] UCSF Helen Diller Family Comprehensive Cancer Center
- [ ] UCSF Langley Porter Psychiatric Institute (LPPI)
- [x] UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)
- [x] UCSF Mount Zion
- [x] UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- [ ] UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals and clinics)
- [ ] Fresno - UCSF Fresno OR Community Medical Center (CMC)
- [ ] Gladstone Institutes
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)
- [x] Zuckerberg San Francisco General (ZSFG)

Research involving ZSFG: You are required to obtain additional approvals from the ZSFG Dean's Office. Download the ZSFG Protocol Application Form and submit the completed form to the ZSFG Dean's Office.

6.2 LOCATIONS: At what locations will study visits and activities occur:

the study will occur in the operating room of the different locations below;
-Paranssus UCSF
-Mount Zion UCSF
-Mission Bay UCSF
-ZSFG
-UCLA

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- ( ) Yes
- (•) No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program
- [ ] Weill Institute for Neurosciences Translational Research Unit (WIN TRU)

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

○ Yes ◉ No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By **'multi-center trial'** we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

○ Yes ◉ No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAMC, Gladstone, ZSFG) are the coordinating center.

☑ Other UC Campus

☐ Other institution

☐ Other community-based site

☐ Foreign Country

☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.9 OTHER UC COLLABORATORS: Check any other UC campuses with which you are collaborating on this research study:

☐ UC Berkeley
☐ UC Davis
☐ Lawrence Berkeley National Laboratory (LBNL)
☐ UC Irvine
☑ UC Los Angeles
☐ UC Merced
☐ UC Riverside
☐ UC San Diego
☐ UC Santa Barbara
☐ UC Santa Cruz

6.10 UC RELIANCES: Are any of the above UC campuses requesting to rely on UCSF's IRB (check all that apply)?

☑ Yes
☐ No

6.14 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus,

commercial, or institutional):

○ Yes ◉ No

6.15 * RELIANCE AGREEMENT TYPE: (REQUIRED) Under what Reliance Agreement is UCSF being requested to rely:

- ☑ UC MOU
- ☐ SMART IRB
- ☐ Established Consortium Agreement, if applicable
- ☐ Private IRB Master Service Agreement
- ☐ Other (specify below)
- ☐ Unknown

6.18 * UC RELIANCE REGISTRY NUMBER: What is the UC IRB Reliance Registry Number: (REQUIRED)

Study #3515

7.0 Research Plan and Procedures

7.1 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove:

Hypothesis: We hypothesis that the use of Norepinephrine will be superior to the use of phenylephrine to correct hypotension induced by general anesthesia

7.2 AIMS: List the specific aims:

With this pilot pragmatic trial, integrated in a larger program, we want to investigate the impact of using NE or PE on post-operative events in patients undergoing major surgery with general anesthesia and needing vasopressors infusion to maintain their systemic arterial pressure. We hypothesize that NE will be superior to PE when used as the primary vasopressor and reduce the incidence of major adverse events after surgery.

1. Our aim is to test the **logistics** of the electronic health record-embedded, cluster randomized, multiple-crossover design[5] for a future larger multi-center trial, including our ability **to separate the use of vasopressors** between study groups.
2. The sub-aim of this pilot trial is to ***estimate the average treatment effect*** of each vasopressors on secondary outcomes and ***heterogeneity in treatment effect***(HTE) of NE vs PE among subgroups or clusters of patients to inform the design of a future larger trial.

The primary endpoint will be the separation between study groups in the first line vasopressor administration (% in type of vasopressor in each groups). Secondary endpoints will include:

- Death within 30 days
- Acute kidney injury defined by the KDIGO definition
- Severe acute kidney injury (stage 2 or 3 of the KDIGO definition)
- Myocardial Injury following non-cardiac surgery (MINS)
- Adverse cardio-renal events
- Hospital length of stay
- Rehospitalization within 30 days

7.3 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

Design: pragmatic, cluster-randomized, open-labeled, multiple-crossover trial across hospital from University of California, San Francisco (UCSF) and University of California, Los Angeles (UCLA). Centers will be assigned to use either PE or NE for the first-line intravenous infusion of vasopressor in the OR (similar to Table 1, with 2 extra months). Centers will be randomly assigned to use PE during even-numbered months and NE during odd-numbered months, or vice versa. We will be using data collected in routine clinical care and automatically extracted from the electronic health record (EHR).

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
UCSF Parnassus	NE	PE	NE	PE	NE	PE
UCSF Mission Bay	PE	NE	PE	NE	PE	NE
UCSF Mt. Zion	NE	PE	NE	PE	NE	PE
ZSFG	PE	NE	PE	NE	PE	NE
UCLA Ronald Reagan	NE	PE	NE	PE	NE	PE

Table 1. distribution of clusters during the trial

7.4 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

50 million patients undergo surgery each year in the United States. Postoperative mortality is considered the third leading cause of death worldwide[6]. Hemodynamic instability and specifically hypotension during surgery have been linked to increased postoperative morbidity and mortality. Avoiding hypotension during surgery on the other hand has been shown to improve outcome of surgical patients. Episodes of hypotension during surgery are associated with an increased risk of acute kidney injury, stroke, cardiac events and death[7]. Treating or preventing hypotension during general anesthesia and major surgery was found to improve outcomes[8]. Futier et al. reported a lower incidence of post-operative major events (i.e. post-operative organ dysfunction) in patients randomized in an individualized strategy to maintain baseline arterial pressure (using

norepinephrine) to a control group with standard of care[9]. This has led to an increased use of vasopressors over recent years (Figure 1). At this time, it is unclear what is the best vasopressor to maintain blood pressure during surgery.

***Figure 1**. Proportion of adult patients undergoing major non-cardiac surgery under general anesthesia in 45 centers in the US, and receiving continuous infusion of vasopressors over 4 periods between 2002 and 2020. Data extracted from 6,742,273 patients from the MPOG cohort.*

Hypotension during anesthesia and surgery is commonly treated with vasopressors such as phenylephrine (PE), a synthetic pure vasoconstrictor, or norepinephrine (NE), which has both inotropic and vasoconstrictor activity[10,11]. NE increases cardiac output and increases cardio-vascular coupling due to b-agonist effects compared to PE, a purely vasoconstrictive agent. The pure vasoconstrictive effects of phenylephrine have however been a concern. In septic patients, the use of phenylephrine over norepinephrine during a shortage of the second was associated with an increased risk of death[12]. Norepinephrine also increases renal blood flow in distributive shock, a potential mechanism underlying improved outcomes[13,14,15]. While maintaining the arterial pressure and organ perfusion pressure is expected to maintain organ perfusion and decrease the risk of organ failures post-operatively, NE increases cardiac output and cardiovascular coupling through b-adrenergic signaling, whereas PE does not. Of note, a strategy of optimizing cardiac output during major surgery was suggested to improve post-operative outcomes[16].

Finally, infusion of NE at a low concentration in a peripheral venous line has been shown to be safe and effective in restoring the mean arterial pressure during anesthesia[17].

Given the number of patients undergoing general anesthesia and being treated with vasopressors worldwide each year, and the burden of post-operative major events and death, we do believe

that the choice of vasopressors during general anesthesia represent a major unaddressed question which needs to be now investigated. Even though the choice of vasopressors is likely to impact outcomes this remains to be proven.

7.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

No study have yet investigated the impact of using phenylephrine or norepinephrine on post-operative cardiovascular outcomes after general anesthesia. The available preliminary studies are summarized below (see references) :
1) Admininstration of norepinephrine to correct hypotension during spinal anesthesia is a safe alternative to phenylephrine.
2) Adminsitration of norepinephrine during general anesthesia is associated with a decrease of vascular compliance to a lesser extent then phenyephrine
3) Administration of norepinephrine using a peripheral intravenous line is safe and not associated with local or systemic complications
4) Preventing hypotension during general anesthesia using norepinephrine is associated with a lower risk of post-operative organ failure compared to standard of care.

One major limitation on the choice of vasopressors has been the lack of data on their impact on outcomes after major surgery. Given the number of patients undergoing major surgery each year in the US, reducing complications by improving vasopressor selection will improve individual health, improve public health, and reduce costs. The design of VEGA-1 is innovative – it will be among the first pragmatic trials to address a major question in perioperative medicine: investigating a strategy to improve postoperative outcomes and allow better understanding of the use of vasopressors in the surgical setting. On top of being the **first to address this question**, this trial is innovative for three reasons:

1. **The principal barrier** for exploring the consequences of vasopressors on clinically important outcomes has been the need for a large sample size to detect effect sizes of small absolute magnitude. We will overcome this limit using the **cluster cross-over randomized controlled**. This design has already been used, mostly in the field of critical care medicine[18]. The potential of this trial design remains largely untapped in the field of peri-operative medicine. We strongly believe that the cluster cross-over randomized trial is the most appropriate design for addressing this question for several reasons:
    a. First, it is difficult to predict *a priori* which patients will require infusion of a vasopressor to maintain their arterial pressure. It is therefore highly difficult to individually enroll a patient before this criterion for inclusion is met.
    b. Second, this design is highly relevant to compare different routinely used practices (as NE or PE infusion during general anesthesia). It allows better trial efficiency and enrollment of large cohorts, and therefore increases the power of the study.
    c. Finally, by limiting the number of patients non-included, this design increases the ability to generate evidence relevant to the actual practice environment. In other words, it increases the generalizability of the results.

2. We will also use a highly efficient **registry-embedded design** using the electronic medical record. This will limit time and resource burden and once again increase our ability to enroll a maximum number of patients.

3. We will use innovative statistical methodology, including **Heterogeneity in Treatment Effect (HTE)** analysis and machine learning approaches. This will aid identification of patient subgroups likely to derive maximum benefit. Estimating HTE among subgroups or clusters of patients will enable us to identify the potential benefit of one drug over the other based on individual or group characteristics, permitting refinement of the population of interest for future larger trial (VEGA-2).

Combining **the cluster-randomized cross-over design with HTE analysis** will overcome the major limitations and barriers we face in peri-operative medicine.

7.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

7.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

( ) Yes (•) No

If you are not sure if your study involves billable procedures, send an email to the UCSF Office of Clinical Research (OCR) for help answering this question.

7.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [ ] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Social media-based research activities
- [ ] Observation
- [ ] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [x] Randomization to one intervention versus another
- [ ] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

7.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring

- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Hospitals will be assigned to use either PE or NE for the first-line intravenous infusion of vasopressor in the OR. Centers will be randomly assigned to use PE during even-numbered months and NE during odd-numbered months, or vice versa. We will be using data collected in routine clinical care and electronically extracted from the electronic health record (EHR). No additional lab test or procedure will be required for the study. Only the randomisation (of the hospital for each month) will be different from usual care.

Drugs: Phenylephrine 100-200 mcg/ml and Norepinephrine 8-32 mcg/ml[17]. Anesthesia providers will use the concentration that their respective center already uses in line with standard local anesthesia and pharmacy standard of care practices. Anesthesia providers will be encouraged to maintain mean arterial pressure within 20% of baseline values[24]. Of note, the anesthesia provider could use the alternative vasopressor if they consider the benefit of one drug being higher. A second line vasopressor will be allowed.

Design: pragmatic, cluster-randomized, open-labeled, multiple-crossover trial across hospital from University of California, San Francisco (UCSF) and University of California, Los Angeles (UCLA). Centers will be assigned to use either PE or NE for the first-line intravenous infusion of vasopressor in the OR (Table 1). Centers will be randomly assigned to use PE during even-numbered months and NE during odd-numbered months, or vice versa. We will be using data collected in routine clinical care and automatically extracted from the electronic health record (EHR).

Anesthesiologists will provide standard of care during the intraoperative period. They will evaluate the need for vasopressors based on hemodynamic assessment and the arterial pressures goals during the procedure. A general recommendation will be to maintain the mean arterial pressure within 20% from baseline. But the arterial pressure targets can be adjusted on an individual basis, for instance during pre-surgical time-out, or based on individual assessment. Doses of continuous infusion of vasopressors will be adjusted to reach these goals on an individual basis. The choice of the first line vasopressors will be determined by the randomization block.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
UCSF Parnassus	NE	PE	NE	PE	NE	PE
UCSF Mission Bay	PE	NE	PE	NE	PE	NE
UCSF Mt. Zion	NE	PE	NE	PE	NE	PE
ZSFG	PE	NE	PE	NE	PE	NE
UCLA Ronald Reagan	NE	PE	NE	PE	NE	PE

Table 1. distribution of clusters during the trial

7.10 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally:

The study differs from standard clinical practive only by the randomisation of the hospital for each month (Hospitals will be randomized in this cluster trial, no patients). No additional lab test, procedure, or follow-up will be required for the study. All data will be collected from the eHR at the end of the study period.

7.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

○ Yes ◉ No

7.13 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

The goals of the statistical analysis will be to 1) **estimate the difference in the proportion of use of vasopressors between study groups**, 2) ***estimate the average treatment effect*, and 3)** assess the existence of a substantial ***heterogeneity in treatment effect*** (HTE).

1. Proportion of first line vasopressor administered between study groups

The primary goal of this pilot is to verify that the proposed protocol will result in sufficient difference in the proportion of vasopressor used between study groups. For the future large multicenter RCT to be interpretable, we consider that the protocol will need to reach 80% use of norepinephrine in the NE arm versus 20% maximum in the PE arm.

2. *Average Treatment Effect Estimation*

a. The average treatment effect will first be estimated using an adjusted comparison of the prevalence of the secondary outcomes in the two groups. The first vasopressor infusion administered in each eligible case will be recorded to assess the primary outcome and measure compliance within the cluster. Secondary outcomes will be analyzed using generalized, linear, mixed-effects models. Assigned vasopressor, age, sex, racial identity, ethnicity, surgical service, home medications (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), comorbidities (preoperative hypertension, diabetes, congestive heart failure, and coronary artery disease), number of norepinephrine boluses, number of phenylephrine boluses, and total number of unique vasopressors administered via infusion will be included in this model as fixed effects, and the center the surgery occurred at was included as a random intercept. Data will b analyzed using R version 4.1.3 and Python 3.6.8. Continuous variables were described using mean (standard deviation) or median (Q1-Q3) as appropriate. Categorical variables were described using count (percentage). Results will be reported on intention-to-treat and per-protocol analysis. We prespecified subgroups to explore heterogeneity of treatment based on age (≥65), comorbidities (hypertension, diabetes, heart failure, and chronic kidney disease), home medications (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers), type of surgery (abdominal and pelvic surgery, neurological surgery), and EBL>300 ml.
b. In addition, since the benefit of adjusting on confounders was clearly reported for randomized controlled trial, we are planning to estimate the adjusted average treatment effect using a semi-parametric machine-learning based estimator, called targeted machine learning estimator (TMLE) in an ancillary study.

3. *Heterogeneity in Treatment Effect (ancillary study)*

To best define inclusion criteria and subgroup analyses in a forthcoming larger multicenter randomized controlled trial, the proposed protocol also aims at quantifying het-erogeneity of treatment effects (HTE) across clusters of patients. This information will be instrumental in better defining the inclusion criteria for a larger trial and also in defining the a priori probability distribution in the overall population, as well as in subgroups since we are planning to use a Bayesian approach to analyze the results of the larger trial. In order to avoid multiple prespecified subgroup analyses, HTE will be estimated across clusters defined in a data-driven way. Specifically, we are planning to identify in the sample cnumber of clusters using k-means for mixed large data[25]. Clustering will be done on the following data, as they are clinically considered to be potential effect modifiers: Age, hypertension, diabetes, heart failure, chronic kidney disease, stroke, home medications (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers), pre-operative hemoglobin level, type of surgery. Heterogeneity across clusters will be tested by estimating the treatment effect within each cluster and testing the interaction between treatment effect and cluster using the Gail and Simon qualitative and quantitative interaction test[26].

Sample size: With 500 to 1000 surgical cases requiring vasopressors with surgery>2 hours every month, we plan to conduct the pilot trial for 6 months (for each cluster), allowing the recruitment of at least 2000 patients, which ever comes first. Such a sample size will allow us to:

i. Detect a difference in the proportion of NE use between arms greater than 60% (i.e. 80% NE use in the NE arm vs 20 % in the PE arm), corresponding to a 80% compliance to the protocol, with a 0.03 bound of the 95% confidence interval on each side
ii. Meaning that any difference of the proportion of use of NE greater than 0.63 will be associated with a lower bound of the 95%CI greater than 0.60 and thus will allow to reject the null hypothesis (difference in proportion not greater than 60%)

7.14 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

1. Semler MW, Self WH, Wanderer JP *et al.* Balanced Crystalloids versus Saline in Critically Ill Adults. *N. Engl. J. Med.* 2018; **378**: 829–839.

2. Khanna AK, Maheshwari K, Mao G *et al.* Association Between Mean Arterial Pressure and Acute Kidney Injury and a Composite of Myocardial Injury and Mortality in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. *Crit. Care Med.* 2019; **47**: 910–917.

3. Mets B. Should Norepinephrine, Rather than Phenylephrine, Be Considered the Primary Vasopressor in Anesthetic Practice? *Anesth. Analg.* 2016; **122**: 1707–1714.

4. Vallée F, Passouant O, Le Gall A *et al.* Norepinephrine reduces arterial compliance less than phenylephrine when treating general anesthesia-induced arterial hypotension. *Acta Anaesthesiol. Scand.* 2017; **61**: 590–600.

5. Vallejo MC, Attaallah AF, Elzamzamy OM *et al.* An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. *Int. J. Obstet. Anesth.* 2017; **29**: 18–25.

6. Habib AS. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. *Anesth. Analg.* 2012; **114**: 377–390.

7. McIlroy DR, Bellomo R, Billings FT *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: renal endpoints. *Br. J. Anaesth.* 2018; **121**: 1013–1024.

8. Futier E, Lefrant J-Y, Guinot P-G *et al.* Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA* 2017; **318**: 1346–1357.

9. Pancaro C, Shah N, Pasma W *et al.* Risk of Major Complications After Perioperative Norepinephrine Infusion Through Peripheral Intravenous Lines in a Multicenter Study. *Anesth. Analg.* 2019.

10. Viechtbauer W, Smits L, Kotz D *et al.*A simple formula for the calculation of sample size in pilot studies. *J. Clin. Epidemiol.*2015; **68**: 1375–1379.

8.0 Drugs and Devices

8.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

(•) Yes ( ) No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

Very few studies involving drugs qualify for Expedited Review. Please go back to Section 4.0 Initial Screening Questions and change your answer to 4.6 to 'Greater than Minimal Risk' and 4.7 to 'Full Committee. It will be reviewed under an Expedited Review procedure if the IRB determines it qualifies as such. Your IRB approval letter will note the Level of Review and Risk Assigned.

8.2 LIST THE DRUGS OR BIOLOGICS: List the drugs or biologics that will be studied. In the drug details screen you will be asked questions such as:

- **Whether the drug or biologic is FDA approved**
- **If the drug or biologic will be provided at no cost**
- **If an IND is necessary, the IND number, and who holds the IND**
- **If the drug or biologic is FDA approved and an IND is not required, the rationale for the decision**
- **If the Investigational Drug Service (IDS) is dispensing the drug or biologic (required unless a waiver is obtained from the IDS)**

Please see the UCSF IRB website for more details about the use of drugs and biologics in research, including the IND Decision Worksheet. Verification of IND numbers: If the sponsor's protocol does not list the IND number, you must submit documentation from the sponsor or FDA identifying the IND number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this drug or biologic, please attach it to the application.

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** LEVOPHED **Generic Drug Name:** NOREPINEPHRINE BITARTRATE **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	LEVOPHED
Generic Drug Name:	NOREPINEPHRINE BITARTRATE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Norepinephrine

Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** phenylephrine **Generic Drug Name:** phenylephrine **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	phenylephrine
Generic Drug Name:	phenylephrine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Pharmacy
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	

Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

8.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

8.6 * EXPANDED ACCESS: Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

9.0 Sample Size and Eligibility Criteria

9.1 ENROLLMENT TARGET: How many people will you enroll:

2000

If there are multiple participant groups, indicate how many people will be in each group:

2000 patients (1000 patients in each group).

9.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Sample size: With 500 to 1000 surgical cases requiring vasopressors with surgery>2 hours every month, we plan to conduct the pilot trial for 6 months, allowing the recruitment of at least 2000 patients, or whichever comes first. Such a sample size will allow us to:

i. Detect a difference in the proportion of NE use between arms greater than 60% (i.e. 80% NE use in the NE arm vs 20 % in the PE arm), corresponding to a 80% compliance to the protocol, with a 0.03 bound of the 95% confidence interval on each side
ii. Meaning that any difference of the proportion of use of NE greater than 0.63 will be associated with a lower bound of the 95%CI greater than 0.60 and thus will allow to reject the null hypothesis (difference in proportion not greater than 60%)

9.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

☐ 0-6 years
☐ 7-12 years
☐ 13-17 years
☑ 18-64 years

☑ 65+

9.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

☑ Inpatients
☐ Outpatients
☐ Family members or caregivers
☐ Providers
☐ People who have a condition but who are not being seen as patients
☐ Healthy volunteers
☐ Students
☐ Staff of UCSF or affiliated institutions
☐ None of the above

9.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

☐ Children / Minors
☑ Adult subjects unable to consent for themselves
☑ Adult subjects unable to consent for themselves (emergency setting)
☑ Subjects with diminished capacity to consent
☐ Subjects unable to read, speak or understand English
☐ Pregnant women
☐ Fetuses
☐ Neonates
☐ Prisoners
☑ Economically or educationally disadvantaged persons
☐ None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

A large percentage of the population at SFGH, one of our study sites, has individuals who are economically or educationally disadvantaged. The clustered design implies to include the largest population possible at each site to best reflect to usual care provided at each location (i.e. clusters) and ensure the generalizabililty of the results in the clusters.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

The collection of the data from the eHR involves no more than a minimal risk of privacy of individuals.

1. **We have an adequate plan to protect the identifiers from improper use and disclosure. No sensitive data or identifiers will be extracted from the eHR. Only those directly involved in the study will have access to the research records. Data extraction process adheres to UCSF's policy for data access with special focus on the Security and Privacy rules.**

   Regarding the Security Rule:

   We have established a secure, centralized, and standardized process for controlling access to and release of PII/PHI and ensuring access is approved, appropriate and in accordance with the Minimum Necessary Standard. Information will be maintained in a secure environment that meets the UCSF Minimum Security Standards for Electronic Information Resources.

   Individuals responsible for the security of the information at all times are required to comply with all applicable state and federal privacy laws. UCSF's "MyResearch" provides secure, private storage for UCSF research teams. Requesting individuals are recommended to maintain data within UCSF's "MyResearch."

   Regarding the privacy Rule:

   Individual must submit necessary documentation. Information accessed may only be used for its intended and approved purpose. All information will be de-identified to the fullest extent possible and consistent with the Minimum Necessary Standard. Coded data and coded data keys maintained in either hard copy or electronic format will be stored separately. All PII/PHI will be securely destroyed after use or when no longer needed. Approval and Statement of Responsibility will be renewed at least once every two years.

2. **We have an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research: The data extracted from the eHR will be destroyed when no longer needed (expected after 10 years after the study has been completed). This time frame is standard to allow verification of the data analysis if any question arises after the manuscripts have been authored. Computer files will be deleted, and hard copy materials will then be discarded. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.**
3. **We have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity: The data will not be shared with any other person or entity (except as required by law) directly involved in the study. PHI gathered throughout the course of this study will not be used or disclosed for any purpose other than this specific research study.**

B. The research could not practicably be conducted without the waiver or alteration; and

REPLY: this research which implies enrolling a very large number of patients with very large inclusion criteria would not be feasible without a waiver of consent. It would be impossible to enroll such a large number of patients in a limited period of time. Furthermore, the selection of patients due to the consent would lead to unbalanced clusters making the study impossible to interpret.

C. The research could not practicably be conducted without access to and use of the protected health information.

REPLY: The research could not practicably be conducted without access to and use of the protected health information for collecting outcomes. The health information collected will be through the eHR and standard of care, without further patient contact.

9.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

Inclusion criteria:

-age 18 Years and older

-Surgery under general anesthesia and requiring infusion of vasopressors to maintain the mean arterial pressure.

-Surgery duration>2 hours

9.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

Exclusion criteria:

-cardiac surgery

-patients on ECMO

-outpatient (come-and-go surgery)

-obstetric procedures

-patient already receiving NE or PE before induction of anesthesia

-patients transferred immediately (i.e. within 24 hours) after surgery to another hospital.

-solid organ transplant (kidney, liver, pancreas)

-Patients with severe trauma

9.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

◉ Yes ○ No

Attach a letter of acknowledgement for the study from the involved patient care manager. If you don't know who the patient care manager is, click here to send an email to the nursing group.

9.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

○ Yes ◉ No

10.0 Recruitment and Consent

10.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

○ Yes ◉ No

10.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- [x] Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- [ ] Already approved recruitment registry
- [ ] Re-contact of participants from the investigators' previous studies
- [ ] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool (describe below)
- [ ] CTSI Recruitment Services unit
- [ ] Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- [ ] Other method (describe below)

* Provide details about the subject identification methods: **(REQUIRED)**

The primary endpoint of this pilot trial is to investigate the separation of vasopressor used (i.e. norepinephrine vs phenylephrine) between the two groups. The population of interest will be selected using CaseView, a secure system accessible by all anesthesiologists through APeX that is used for viewing the daily OR schedule and based on the data available in the eHR.

10.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [ ] Investigators' own patients or patients seen within the same practice
- [ ] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [x] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [ ] Other method (describe below)

10.4 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

The eligibility will be determined a posteriori sing CaseView, a secure system accessible by all anesthesiologists through APeX that is used for viewing the daily OR schedule and based on the data available in the eHR (by the CTSI).

10.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [ ] Potential participant
- [x] Other (explain below)

Provide details about how contact is initiated:

There will be no contact of patients or selection of patients by the investigators. The population of interest will be selected by the CTSI a posteriori based on the data available in the eHR.
The providers will be contacted by the investigators team (principal investigators and reseach coordinators)

10.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [ ] In person
- [ ] Phone
- [ ] Letter / email
- [ ] Website or app
- [x] Other (explain below)

10.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

There will be no contact of patients or selection of patients by the investigators. The population of interest will be selected by the CTSI a posteriori based on the data available in the eHR.
The providers will be contacted by the investigators team (principal investigators and reseach coordinators)

10.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [ ] Sign a paper consent form at the end of the consent discussion (signed consent)
- [ ] Sign an electronic consent form using DocuSign (signed consent)
- [ ] Provide online consent through an app, a website, or a survey tool such as Qualtrics or REDCap (waiver of signed consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent - waiver of signed consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent - waiver of signed consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not able to provide consent (emergency medicine, greater than minimal risk waiver/alteration of consent - requires an approved community consultation plan)
- [ ] Not able to provide consent (emergency medicine, minimal risk waiver/alteration of consent)
- [x] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

10.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in

relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

Regarding patients:

Given this, and the nature of the study, we believe it is not necessary to provide the information sheet to patient participants. The primary objective of this study is actually to investigate the providers adhesion to the randomization and the separation of vasopressors between the 2 groups (see below regarding information to providers), and we will be collecting limited PHI about patients.

We ask for a waiver of consent and Authorization to use the PHI for the patient participants. It would be impracticable to conduct the research if consent/authorization to use the PHI will have to be collected. Importantly, the research will meet the criteria for a waiver of authorization under the Privacy Rule as:

- **This research could not practicably be conducted without the requested waiver or alteration (given the design of the study and the large number of patients enrolled).**
- **This research could not practicably be conducted without access to and use of the PHI.**
- **The PHI use or disclosure involves a minimal risk to the privacy of individuals. We have an adequate plan to protect PHI identifiers from improper use and disclosure; an adequate plan to destroy those identifiers at the earliest opportunity, and the PHI will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule (see below).**

a) Regarding the privacy Rule:

1)Plan to protect the identifiers from improper use and disclosure:

No sensitive data or identifiers will be extracted from the eHR. Only those directly involved in the study will have access to the research records. Data extraction process adheres to UCSF's policy for data access with special focus on the Security and Privacy rules.

-Information accessed may only be used for its intended and approved purpose. All information will be de-identified to the fullest extent possible and consistent with the Minimum Necessary Standard. Coded data and coded data keys maintained in either hard copy or electronic format will be stored separately. All PII/PHI will be securely destroyed after use or when no longer needed.

2)We have an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research: The data extracted from the eHR will be destroyed when no longer needed (expected after 10 years after the study has been completed). This time frame is standard to allow verification of the data analysis if any question arises after the manuscripts have been authored. Computer files will be deleted, and hard copy materials will then be discarded. At critical junctures of the protocol (e. g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

3)The protected health information will not be reused or disclosed to any other person or entity: The data will not be shared with any other person or entity (except as required by law) directly involved in the study. PHI gathered throughout the course of this study will not be used or disclosed for any purpose other than this specific research study.

b. **Regarding the Security Rule:**

-The CTSI has established a secure, centralized, and standardized process for controlling access to and release of PII/PHI and ensuring access is approved, appropriate and in accordance with the Minimum Necessary Standard. Information will be maintained in a secure environment that meets the UCSF Minimum Security Standards for Electronic Information Resources.

-Individuals responsible for the security of the information at all times are required to comply with all applicable state and federal privacy laws. UCSF's "MyResearch" provides secure, private storage for UCSF research teams.

Regarding the providers:

An information sheet will be provided to them (see below). While providers can choose to use a different vasopressor than the "vasopressor of the month" based on their clinical judgement, doing so does not mean they are no longer part of the study, since these data are included regardless.

However, providers do no meet the definition of human subjects in this study as:

-We won't obtain information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens;

-We won't obtain, use, study, analyze, or generate identifiable private information or identifiable biospecimens.

The PI and/or Co-PIs will explain the Study Protocol at Anesthesia Grand Rounds, through emails and smaller group information meetings. Volunteer providers (MD anesthesiologists, CRNAs and residents) will be requested. Questions will be invited and answered, including a clear description of what data is being collected (through the eHR, with no personal identifiers).

Phenylephrine and norepinephrine are two vasopressors currently used in the routine care of patients in he operating room at UCSF and around the world. Currently, no high-quality data suggest that choice of one vasopressor over another affects clinical outcomes among surgical adult patients. During the VEGA trial, each time a vasopressor will be ordered, the study will be confirming that the treating clinician does not feel that a specific vasopressor is required for the safe treatment of that specific patient at that specific point in time. The trial is felt to pose minimal risk because (1) exposure to the study vasopressors occurred only for patients whose anesthesia providers had already decided to administer an IV vasopressor, (2) the vasopressors examined are already used in routine practice in the study environment, (3) no definitive prior data suggested clinical outcomes is better with one vasopressor relative to the other, and (4) the study will be confirming with every vasopressor order that the providers don't not feel any one vasopressor is required for safe treatment of that specific patient at that specific time. Given the minimal risk, the focus of the study on vasopressors use at an OR level, as well as the impracticability of consenting each patient undergoing surgery prior to the first administration of vasopressor (i.e. we don't know a priori who will require a vasopressor infusion during general anesthesia), we request a waiver consent to be granted by the Institutional Review Board. This approcah has been successfully used in alternative settings (DOI: 10.1056/NEJMoa1711586 and DOI: 10.1056/NEJMoa1711584).

Secondary endpoints will be collected throught the eHR through routinely collected data and no sensitive information.

10.14 TIME: What is the estimated time commitment for participants (per visit and in total):

The estimated time commitement for participants (providers) is the duration of the anesthesia procedure (betweeen 2 hours and 10 hours for most procedures). Treatments and follow-up (throught the EHR system) will be part of the standard current practice and will not add any time.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

10.15 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

(•) Yes ( ) No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

The protocol we submit is aligned with standard of care. Only the randomization of the different locations will differ from standard of care. Regarding the use of vasopressors, if the anesthesia provider decides to introduce a vasopressor and the patient is not enrolled, Phenylephrine or norepinephrine can be used, based on the choice of the anesthesia provider. The choice of the first line vasopressor will be determined by the randomization block. If the patient remains hypotensive, second- and third-line vasopressors will be allowed; this will be at the discretion of the anesthesiologist. If the anesthesiologist does not "like" or "prefer" the vasopressor assigned for the month or strongly believes the patient requires one vasopressor over another, he or she has the authority to override the randomization. This study is a pilot study with separation of treatment administration being the primary endpoint. Therefore, in both the above scenarios, the patient will not be excluded from the analysis (intention to treat analysis) for the primary endpoint. We will, however, do a per-protocol analysis for secondary endpoints.

10.16 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

(•) Yes
( ) No
( ) Not applicable

11.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

11.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

(•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

11.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

11.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

◉ Yes

If **no**, a waiver of authorization can NOT be granted.

11.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- ☐ Names
- ☐ Dates
- ☐ Postal addresses
- ☐ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☐ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers
- ☐ Biometric identifiers
- ☐ Facial photos or other identifiable images
- ☐ Any other unique identifier
- ☑ None

Note: HIPAA rules require that you collect the minimum necessary.

11.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

none

Note: HIPAA requires that you collect the minimum necessary.

11.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

No data will be collected to deternine eligibility for recruitement.

12.0 Waiver of Consent and/or Waiver of Authorization (Including for Minimal Risk Procedures in Emergency Setting)

(2020)

12.1 * IMPACT OF WAIVER ON RIGHTS AND WELFARE: I affirm that subjects' rights and welfare will not be adversely affected by waiving informed consent:

◉ Yes

12.2 * PRACTICABILITY: It is not practicable to conduct the research without the waiver of consent / authorization because (check all that apply):

- ☐ Many subjects are no longer being followed at the institution or are deceased
- ☑ The attempt to contact subjects poses a greater risk than this study
- ☑ The large number of records required makes it impracticable to contact all potential subjects
- ☐ The researchers do not know the identity of the study subjects and therefore cannot contact them
- ☐ The data being used was collected under a different IRB-approved study and subjects gave their consent for data to be used in research of this type
- ☐ The patients will be unconscious and we are requesting a temporary waiver of consent /authorization for a minimal risk procedure such as a blood draw

12.3 * INFORMING SUBJECTS POST-PARTICIPATION: Will subjects be provided with pertinent information after their participation:

○ Yes ◉ No

12.4 * IDENTIFIERS: Are you recording identifiers in the research records: (REQUIRED)

○ Yes ◉ No

13.0 Risks and Benefits

13.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- ☑ For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- ☐ Risks associated with radiation exposure for imaging studies specifically for research purposes
- ☐ Risks associated with the administration of contrast agent for imaging studies
- ☐ Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- ☐ For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- ☐ For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- ☐ Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- ☐ Risk of pain or physical discomfort caused by the research intervention
- ☐ Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

The choice of the first line vasopressor will be determined by the randomization block. If anesthesiologist does not agree with randomized choice of the month, they can opt to use the vasopressor of their choice while following best standard of care. If the patient remains hypotensive, second- and thirdline vasopressors will be allowed; this will be at the discretion of the anesthesiologist. If the anesthesiologist does not "like" or "prefer" the vasopressor assigned for the month or strongly believes the patient requires one vasopressor over another, he or she has the authority to override the randomization.

13.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

The known risks related to the vasopressor infusions (hypertension, cardiac arrhythmia) are independent of the risk of the protocol and no greater than if the patient were not participating in the study.

13.3 MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

We will minimize risks by ensuring the following strategies:

1) best standard of care will be applied when using the drugs, including

-close hemodyanmic monitoring to adjsut the perfusion rate to control the systemic arterial pressure,

-standard drug dilutions will be used to minimize the risk of side effects in case of bolus and/or extravascular diffusion

-dedicated line for vasopressors to prevent any bolus

-verification of good permeability and absence of subcutaneous diffusion before infusion of the vasopressor

-a certified provider (anesthesiologist and/or CRNA) will be present at all time to ensure security of the perfusion

2) confirming with every vasopressor order that the providers do not feel that any one vasopressor is preferred for safe treatment of that specific patient at that specific time

13.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

Even though the risk of this trial comparaing two standard-of-care drugs that are already in use is

minimal, the safety of the participants will be ensured by:

1) the presence at all times of an anesthesiologist or CRNA trained in the use of these medications

2) standard of care surveillance after drug adminstration during surgery in the Post-Anesthesia Care Unit (PACU) or the intensive care unit (ICU) as appropriate

3) critical resources are available in all facilities participating to the study

13.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [ ] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [ ] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

13.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

The benefit appears to largely outweigh the risk. As stated before, the two drugs are commonly used as standard of care. The study will not add any time burden to the patients due to the use of the electronic medical record to collect outcomes. Including a large number of patients will however allow us to detect potential small differences in in the outcomes between the two vasopressors and inform us on the best practice for correcting hypotension during general anesthesia.

The risk for providers is minimum since both drugs are routinely adminstered in the OR.

14.0 Confidentiality, Privacy, and Data Security

14.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [ ] Conduct conversations about the research in a private room
- [ ] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [x] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

14.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

- ( ) Yes
- (•) No

14.3 SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

- ( ) Yes
- (•) No

14.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

Medical records will be accessed in electronic format only, through APeX using a secure campus computer or an encrypted computer through VPN/Junos Pulse. A list of names/MRNs for enrolled participants will be kept as a Patient List on APEX itself (using the PI, Dr. Legrand's account). Dr. Legrand's laptop and desktop are encrypted and managed by Anesthesia IT. Additional, de-identified study data will be extracted from APeX directly into a secure database. Collaborative, de-identified data for this study will be stored in the secure environment of UCSF Box or MyResearch. A de-identified digital key, or unique alphanumeric code correlated with the subjects' name, date of birth, MRN, and diagnosis, will be stored only within the UCSF MyResearch secure environment.

14.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

○ Yes ◉ No

14.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality:

○ Yes ◉ No

14.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

○ Yes ◉ No

14.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- ☑ Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- ☐ Added to the hospital or clinical medical record
- ☐ Created or collected as part of health care
- ☐ Used to make health care decisions
- ☐ Obtained from the subject, including interviews, questionnaires
- ☐ Obtained ONLY from a foreign country or countries
- ☐ Obtained ONLY from records open to the public
- ☐ Obtained from existing research records
- ☐ None of the above
- ☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH

In addition to signing a consent form, each subject will have to sign the UCSF Research Subject Authorization Form (HIPAA Form). Upload the HIPAA Authorization Form in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits. Please call the IRB office at 415-476-1814 if you have questions about HIPAA research requirements.

If derived from a medical record, identify source:

Apex

14.10 * IDENTIFIERS: Check all identifiers that will be collected and included in the research records, even temporarily: (REQUIRED)

- [ ] Names
- [x] Dates
- [ ] Postal addresses (if only requesting/receiving zip codes check Yes to the Zip Code question below instead of checking this box)
- [ ] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [ ] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [x] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

○ Yes ◉ No

14.11 * ZIP CODES: Some research data sets include zip codes. Will you be receiving data with zip codes as the only portion of an address: (REQUIRED)

Checking 'Yes' here means that you will not be requesting access to any other data element of a patient's address. If you are requesting other parts of an address such as street names and address numbers, check 'No' here and check the box for 'Postal addresses' in the list of 18 PHI Identifiers in the previous question.

○ Yes ◉ No

14.12 * PATIENT MEDICAL RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

◉ Yes ○ No

14.13 * CLINICAL DATA - GENERAL DESCRIPTION: Provide a general description of the types of clinical data that you are requesting access to: (REQUIRED)

-Demographics,
-type if surgery
-Anesthesia techniques
- first line vasopressor administration (% of cases with appropriate vasopressor with respect to group attribution).
-Major adverse cardiovascular and renal events (combined endpoint of death, myocardial infarction, stroke, acute decompensated heart failure and acute kidney injury)

- Hospital length of stay

- serum creatinine

- Major adverse kidney events (combined endpoint of death and/or dialysis and/or non recovery from acute kidney injury at hospital discharge).

- Surgical complication requiring a new surgical procedure

- Rehospitalization within 30 days

14.14 * CHART/CLINIC NOTES AND OTHER FREE TEXT FIELDS: Will the medical record data include any information extracted from free text fields: (REQUIRED)

○ Yes ◉ No

14.15 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

☐ Drug or alcohol abuse, diagnosis or treatment
☐ HIV/AIDS testing information
☐ Genetic testing information
☐ Mental health diagnosis or treatment
☑ None of the above

14.16 * ACCESS TO OTHER SENSITIVE OR PROTECTED DATA: Are you requesting access to any sensitive health data not protected under HIPAA (any other health history that patients would expect to be kept private such as records relating to treatment for obesity, STDs, compulsive behaviors, embarrassing health conditions, sexual orientation and practices, etc.): (REQUIRED)

○ Yes ◉ No

14.18 * IDENTIFIABILITY OF FINAL DATA SET: (REQUIRED)

Which type of data set are you requesting IRB approval for:

A de-identified data set does not include ANY of the 18 HIPAA identifiers in the list above or any free text fields.
A limited data set (LDS) is described as health information that excludes direct identifiers but that may include:

- City
- State
- ZIP Code
- Elements of date (including dates such as admission, discharge, service, month and year)
- Other numbers, characteristics, or codes not listed as direct identifiers, including ages in years, months or days or hours

Identifiable data sets include direct identifiers and/or information from free text fields.
Review the **HIPAA FAQs on the IRB website** for more details about identifiability of data sets.

◉ De-identified data set
○ Limited data set
○ Identifiable data set without direct identifiers (includes free text fields)

○ Identifiable data set with direct identifiers (may or may not also include free text fields)

14.19 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☐ Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial management portal
- ☐ UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- ☐ Other web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Text Messaging
- ☐ Wearable devices
- ☐ Audio/video recordings
- ☐ Photographs
- ☐ Paper-based (surveys, logs, diaries, etc.)
- ☑ Other:

* Specify what other methods will you use to collect data: **(REQUIRED)**

Data will be collected from the eHR by the CTSI

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- ☐ Study sponsor
- ☑ UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
- ☐ UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
- ☐ Personal devices, such as laptops or tablets that are not owned or managed by UCSF
- ☐ SF VAMC
- ☐ Zuckerberg San Francisco General Hospital
- ☐ Benioff Children's Hospital Oakland
- ☐ Langley Porter Psychiatric Institution
- ☐ Other UCSF affiliate clinic or location (specify below)
- ☐ Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
- ☐ Other academic institution
- ☐ 3rd party vendor (business entity)
- ☐ Other (explain below)

14.20 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

○ Yes ◉ No

14.21 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

○ Yes ◉ No

15.0 Financial Considerations

15.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

○ Yes ◉ No

15.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

○ Yes ◉ No

16.0 Other Approvals and Registrations

16.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

○ Yes ◉ No

16.2 * HUMAN GENE THERAPY: Does this study involve human gene therapy: (REQUIRED)

○ Yes ◉ No

16.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

17.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

17.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title

- Institutional Affiliation (UCSF, SFGH, VAMC, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Bokoch, Michael P, MD PhD	Co-investigator, study monitoring	Dr. Bokoch is an MD PhD and Assistant Professor of Anesthesia and Perioperative Care. He has over 15 years experience in research, and 5 years of experience in clinical research. He is a practicing clinician and attending anesthesiologist. He has worked on several prospective and retrospective clinical studies at UCSF. He has an active California medical license and is a board-certified anesthesiologist. He has Human Subjects Protection Training and Good Clinical Practice Training.

Chen, Lee-Lynn	Co-investigator, study monitoring	Attending anesthesiologist, Human Subjects Protection Training
Dr. Chen, Catherine L, MD, MPH	Co-investigator, study monitoring	Attending anesthesiologist, Human Subjects Protection Training
Dr. Niemann, Claus MD, MD	Co-investigator, study monitoring	Dr. Niemann is an MD and Professor of Anesthesia and Surgery specializing in Transplant Anesthesia. He has over 15 years of experience in clinical research. He has Human Subjects Protection Training and Good Clinical Practice Training.
Dr. Pirracchio, Romain MD PhD	Statistical analysis	Attending anesthesiologist, Human Subjects Protection Training Statistician, affiliated to UC Berkely
Stein, Deborah M	Co-investigator, study monitoring	Attending anesthesiologist, Human Subjects Protection Training
Dr. Whitlock, Elizabeth MD	Co-investigator, study monitoring	Attending anesthesiologist, Human Subjects Protection Training
Fields, Scott M	Co-investigator, Drugs delivery, monitoring	Pharmacist
Li, Fanny	Co-investigator,, Drugs delivery, monitoring	Pharmacist
Dr. Gropper, Michael Allan, MD, PhD	head of department	Attending anesthesiologist and Chair of department. He has over 30 years of experience in research, including many clinical studies.
Mavrothalassitis, Orestes	Co-investigator, study monitoring	Research trainee

Reddy, Nikitha P	Clinical Research coordinator	BA
Bi, Emily	Clinical Research coordinator	BA/BS
Sturgess-DaPrato, Jillene	Clinical Research coordinator	BA/BS
Ansay, Christopher	Medical Student, completed Human Subject training	BA/BS
Kothari, Rishi P	Co-investigator, study monitoring	Attending anesthesiologist, Human Subjects Protection Training
Spinner, Jon D	Data manager	Applications Programmer, Anesthesia
Armstrong, Rachelle L	Data manager	Applications Programmer, Anesthesia
Fong, Nicholas B	Statistical analysis	data analyst, statistician Member of Anesthesia department, UCSF
Jacobson, Adam Z	Data manager	Applications Programmer, Anesthesia Head of IT Anesthesia , UCSF
Joo, Hyundeok	Co-investigator	Medical student, involved in writing and post-hoc analysis
Krone, Sina E	Co-investigator	Medical student, involved in writing and post-hoc analysis
Nguyen, Kevin H	Co-investigator	Medical student, involved in writing and post-hoc analysis

17.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories

were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., VAMC, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role
David Boldt	UCLA	310-267-8694	DBoldt@mednet.ucla.edu	Co-Principal Investigator
Maxime Cannesson	UCLA	310-267-8693	mcannesson@mednet.ucla.edu	Co-Principal Investigator

Please describe the study responsibilities and qualifications of each affiliated person listed above:

Dr. David Boldt is a board-certified anesthesiologist who will serve as the PI at UCLA for the VEGA study.
Dr. Maxime Cannesson is a board-certified anesthesiologist who will serve as the Co- PI at UCLA for the VEGA 1 study.

18.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**, where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

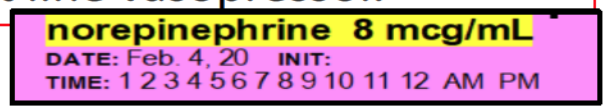
Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.

VEGA-1 trial

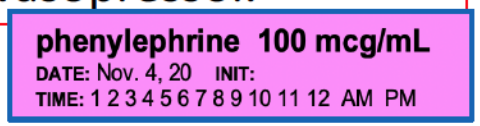
There will be a vasopressor of the month (NE or PE), which will be randomized based on **the study site**. **Each site will rotate the first line vasopressor on the *first day of each month.***

Norepinephrine (NE) 8 mcg/ml (4 mg in 500 ml of NaCl 0.9%) for continuous vasopressor infusion as a first line vasopressor.



OR

phenylephrine (PE) 100 mcg/ml (10 mg in 100 ml NaCl0.9%) for continuous vasopressor infusion as a first line vasopressor.



Patient Inclusion Criteria:

- 18 years or older
- Undergoing surgery with expected duration >2 hours
- Under GA & requiring infusion of vasopressors to maintain MAP

Patient Exclusion Criteria:

- Solid organ transplant (kidney, liver, pancreas)
- Cardiac, obstetric, ECMO, and outpatient procedures
- On vasopressors prior to surgery

	April	May	June	July	August	Sept
UCSF Parnassus	NE	PE	NE	PE	NE	PE
UCSF Mission Bay	PE	NE	PE	NE	PE	NE
UCSF Mt. Zion	NE	PE	NE	PE	NE	PE
ZSFG	PE	NE	PE	NE	PE	NE

Questions? Contact Matthieu.legrand@ucsf.edu; or Michael.Bokoch@ucsf.edu;

atropine 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

succinylcholine 20 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

propofol 10 mg/mL
Expires 8 Hours after:
Mar. 16, 21 TIME: INIT:

propofol 10 mg/mL
Expires 8 Hours after:
Mar. 16, 21 TIME: INIT:

lidocaine 20 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

rocuronium 10 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

norepinephrine 8 mcg/mL
DATE: Mar. 16, 21 TIME: 0700 INIT:
4 mL of 1 mg/mL per 500mL NS

norepinephrine 8 mcg/mL
DATE: Mar. 16, 21 TIME: 0700 INIT:
4 mL of 1 mg/mL per 500mL NS

ePHEDrine 5 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

esmolol 10 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

neostigmine 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

fentaNYL 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

fentaNYL 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

midazolam 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

ceFAZolin 2 gm/10 mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

dexamethasone 4 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

metoprolol 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

ketamine 2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

Drug:
DATE: Mar. 16, 21 INIT:
TIME: 0700

NO MEDS
DATE: Mar. 16, 21 INIT:
TIME: 0700

atropine 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

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DATE: Mar. 16, 21 INIT:
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4 mL of 1 mg/mL per 500mL NS

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DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

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DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

ceFAZolin 2 gm/10 mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

dexamethasone 4 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

etomidate 2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

furosemide 10 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

Drug:
DATE: Mar. 16, 21 INIT:
TIME: 0700

NO MEDS
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

EPINEPHrine 10 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

glycopyrrolate 0.2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

propofol 10 mg/mL
Expires 8 Hours after:
Mar. 16, 21 TIME: INIT:

propofol 10 mg/mL
Expires 8 Hours after:
Mar. 16, 21 TIME: INIT:

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DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

rocuronium 10 mg/mL
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norepinephrine 8 mcg/mL
DATE: Mar. 16, 21 TIME: INIT:
4 mL of 1 mg/mL per 500mL NS

norepinephrine 8 mcg/mL
DATE: Mar. 16, 21 TIME: INIT:
4 mL of 1 mg/mL per 500mL NS

HYDROmorphone 0.2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

labetolol 5 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

sugammadex 100 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

fentaNYL 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

remifentanil 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

midazolam 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

ceFAZolin 2 gm/10 mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

ondansetron 2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

dexmedetomidine 4 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

mannitol 25% (12.5g/50mL)
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

Drug:
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

NO MEDS
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

EPINEPHrine 10 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

glycopyrrolate 0.2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

propofol 10 mg/mL
Expires 8 Hours after:
Mar. 16, 21 TIME: INIT:

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DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

rocuronium 10 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

☆ **VEGA-1 Trial: April 2021** ☆

is "Norepinephrine Month" at Parnassus!

HYDROmorphone 0.2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

labetolol 5 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 0700

sugammadex 100 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

fentaNYL 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

remifentanil 50 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

midazolam 1 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

ceFAZolin 3 gm/10 mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

ondansetron 2 mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

dexmedetomidine 4 mcg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

tranexamic acid 100mg/mL
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

Drug:
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

NO MEDS
DATE: Mar. 16, 21 INIT:
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

The **VEGA study** is assessing whether the choice of vasopressor during general anesthesia impacts surgery outcome.

For the month of **February** at **UCSF Parnassus**, please use **phenylephrine** 100 mcg/ml (10 mg in 100 ml NaCl0.9%) for continuous vasopressor infusion as a first line vasopressor.

phenylephrine 100 mcg/mL
DATE: Nov. 4, 20 **INIT:**
TIME: 1 2 3 4 5 6 7 8 9 10 11 12 AM PM

Patient Inclusion Criteria:

- 18 years or older
- Undergoing surgery with expected duration >2 hours
- Under GA & requiring infusion of vasopressors to maintain MAP

Patient Exclusion Criteria:

- Solid organ transplant (kidney, liver, pancreas)
- Cardiac, ECMO, obstetric, and outpatient procedures
- On vasopressor prior to surgery

Questions? Contact Matthieu Legrand, MD, PhD (**Email:** Matthieu.legrand@ucsf.edu; **Cell:** 628-237-9438) or Michael Bokoch, MD, PhD (**Email:** Michael.Bokoch@ucsf.edu; **Cell:** 650-387-4314).

University of California, Los Angeles

RESEARCH INFORMATION SHEET

The Choice of Vasopressor for Treating Hypotension During General Anesthesia: A Pilot Pragmatic Cluster Cross-over Randomized Trial (Vega-1 Trial)

INTRODUCTION

The Department of Anesthesiology and Perioperative Medicine at the University of California, Los Angeles and San Francisco are conducting a research study. Your participation as you routinely provide anesthesia care for patients undergoing major non-cardiac surgery in this research study is voluntary.

WHY IS THIS RESEARCH BEING DONE?

Hemodynamic instability and specifically hypotension during surgery have been linked to increased postoperative morbidity and mortality. Avoiding hypotension during surgery on the other hand has been shown to improve outcome of surgical patients. Episodes of hypotension during surgery are associated with an increased risk of acute kidney injury, stroke, cardiac events and death[7]. Treating or preventing hypotension during general anesthesia and major surgery was found to improve outcomes[8]. This has led to an increased use of vasopressors over recent years. At this time, it is unclear what is the best vasopressor to maintain blood pressure during surgery.

Hypotension during anesthesia and surgery is commonly treated with vasopressors such as phenylephrine (PE), a synthetic pure vasoconstrictor, or norepinephrine (NE), which has both inotropic and vasoconstrictor activity. NE increases cardiac output and increases cardio-vascular coupling due to β-agonist effects compared to PE, a purely vasoconstrictive agent. The pure vasoconstrictive effects of phenylephrine have however been a concern. In septic patients, the use of phenylephrine over norepinephrine during a shortage of the second was associated with an increased risk of death. Norepinephrine also increases renal blood flow in distributive shock, a potential mechanism underlying improved outcomes. While maintaining the arterial pressure and organ perfusion pressure is expected to maintain organ perfusion and decrease the risk of organ failures post-operatively, NE increases cardiac output and cardiovascular coupling through β-adrenergic signaling, whereas PE does not. Of note, a strategy of optimizing cardiac output during major surgery was suggested to improve post-operative outcomes.

Given the number of patients undergoing general anesthesia and being treated with vasopressors worldwide each year, and the burden of post-operative major events and death, we do believe that the choice of vasopressors during general anesthesia represent a major unaddressed question which needs to be now investigated. Even though the choice of vasopressors is likely to impact outcomes this remains to be proven.

WHICH PATIENTS COULD BE ENROLLED IN THIS RESEARCH STUDY?

All patients 18 Years and older undergoing surgery with an expected duration >2 hours, under general anesthesia and requiring infusion of vasopressors to maintain the mean arterial pressure.

HOW LONG WILL THE RESEARCH LAST AND WHAT WILL I NEED TO DO?

The anticipated duration of the study is 6 months. If you volunteer to participate in this study, the researcher will ask you to do the following:

VEGA-1 is a pragmatic, cluster-randomized, open-labeled, multiple-crossover trial across hospitals from University of California, San Francisco (UCSF) and University of

California, Los Angeles (UCLA). Centers will be assigned to use either Phenylephrine (at a concentration of 100microg/ml) or Norepinephrine (at a concentration of 8 microg/ml) for the first-line intravenous infusion of vasopressor in the OR (Table). Centers will be randomly assigned to use PE during even-numbered months and NE during odd-numbered months, or vice versa. We will be using data collected in routine clinical care and automatically extracted from the electronic health record. In participating in the study, you will **deliver standard of care to the patient**. The only difference will be **that the FIRST LINE vasopressor used for continuous infusion will be determined by the month of randomization of the center** (Norepinephrine or phenylephrine accordingly). The "**vasopressor of the month"** will be announced by email and pagers on the day before the beginning each period, displayed in OR, and other key locations.

	Month 1	Month 2	Month 3	Month 4
Center 1	NE	PE	NE	PE
Center 2	PE	NE	PE	NE
Center 3			NE	PE
Center 4			PE	NE

Of note, the choice of the first line vasopressors will be determined by the randomization block, but the attending anesthesiologist will be allowed to override the randomization if she/he strongly believes the patient requires one vasopressor over another. Also, second- and third-lines vasopressors will be allowed at the discretion of the anesthesiologist if the patient remains hypotensive with the first line vasopressor.

ARE THERE ANY RISKS IF I PARTICIPATE?

There are no anticipated risks to the providers for this study.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

You will not directly benefit from your participation in the research.

The results of the research may improve our understanding of the impact of vasopressors on post-operative outcome and improving our medical knowledge but also contribute to the clinical research of the Department and contribute to its excellence. The results of this study will be the basis of a larger, multicenter, multi-state randomized trial investigating the impact of vasopressors on post-operative outcomes.

What other choices do I have if I choose not to follow the recommendation of the vasopressor of the month?

You may provide standard of care to the patient as you usually do. You can choose to use a different vasopressor than the "vasopressor of the month" based on your clinical judgement if you strongly feel it is more appropriate.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

We will not collect sensitive data or identifiable private information from providers in this study.

How information about you will be stored:
Research data (from the patients) will be stored electronically on a secure network in an encrypted file. Only authorized individuals will have access to it.

People and agencies that will have access to your information:

The research team, authorized UCLA personnel, and collaborators at UCSF, may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

Employees of the University may have access to identifiable information as part of routine processing of your information, such as lab work or processing payment. However, University employees are bound by strict rules of confidentiality.

How long information from the study will be kept:

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WILL I BE PAID FOR MY PARTICIPATION?

You will not be paid for your participation in this research study.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

The research team:
If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact investigators from UCLA: Dr. David Boldt at 310-267-8678 or Claudia Bueno at 310-267-2130 or UCSF, : Dr. Matthieu Legrand at matthieu.legrand@ucsf.edu, Phone: (628)237-9438; Pager: 415-443-9223 or Dr Michael Bokoch at Michael.bokoch@ucsf.edu, (650) 387-4314 or (415) 602-9336.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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University of California, San Francisco

RESEARCH INFORMATION SHEET

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Center 3			NE	PE
Center 4			PE	NE

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