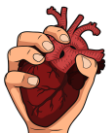


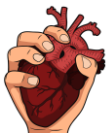
European Society of Anaesthesiology and Intensive Care

Postoperative vasopressor usage: a prospective international observational study

'SQUEEZE'

Protocol V2.0

Short title / Study Identifier	SQUEEZE
Type of Research Project:	Multi-centre Cohort Study
ClinicalTrials.gov ID	NCT03805230
Sponsor/Funder:	European Society of Anaesthesiology and Intensive Care (ESAIC) Rue des Comédiens 24, 1000 Brussels, Belgium Phone: +32 2 743 3290 E-mail: research@esaic.org
Co-Chief Investigators:	Dr Ib Jammer Bergen, Norway Dr Ben Creagh-Brown Guildford, UK



European Society of Anaesthesiology and Intensive Care

ACCESS TO RESEARCH DOCUMENTS

PROTOCOL SIGNATURE SHEET

Co-Chief Investigators		
Name	**Signature**	**Date**
Ib Jammer, Bergen		*06 April 2021*
Ben Creagh-Brown, Guildford		*06 April 2021*
Sponsor: European Society of Anaesthesiology and Intensive Care (24 Rue des Comédiens 1000 Brussels Belgium)		
Pierre Harlet Research and Clinical Trial Coordinator		*06 April 2021*
Local Principal Investigators (enter local details, as applicable)		

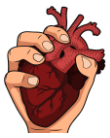
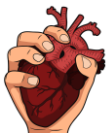


TABLE OF CONTENTS

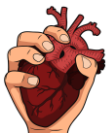
Project Title:	Postoperative vasopressor usage: a prospective international observational study
Short Title:	SQUEEZE
CTGOV ID	NCT03805230
Version/Date:	2.0 / 06 April 2021
Project design:	International prospective observational study
Background and Rationale:	Postoperative hypotension is a common occurrence following major non-cardiac surgery. Receipt of infused vasopressors postoperatively is considered as a surrogate indicator of significant vasodilatation. The incidence of postoperative vasopressor therapy has never been described. There is anecdotal evidence of substantial variation in the management of postoperative hypotension between centres, countries and continents. We hypothesise that there is a variation in the incidence of organ dysfunction, the use of organ support and clinical outcomes in patients treated with postoperative vasopressor therapy.
Objective(s):	Determining what proportion of patients receive postoperative vasopressor infusions, and the incidence of associated organ dysfunction as well as their clinical outcomes. Identifying factors in variation of care (patient, condition, surgery, and intraoperative management), that are associated with receipt of postoperative vasopressor infusions
Outcomes(s):	Primary outcome: Prevalence of postoperative vasopressor usage in a non-cardiac surgical population.
Inclusion / Exclusion criteria:	Inclusion: All adult (≥18 years) non-cardiac surgical patients. Exclusion: Cardiothoracic surgery, obstetric and day case surgery.

Number of Participants:	"Convenience sample" of approximately 40,000 patients for cohort A, 12,800 patients for cohort B.
Project Duration, schedule:	2018 autumn: Electronic survey about current practice and advertising. 2019 spring – 2019 autumn: Recruiting potential investigators. Initiating national ethical approvals. From Autumn 2020: Start inclusion of patients for cohort A and B. From 2022: Data analysis and writing manuscript 2023 Submission of primary research paper.



Abbreviations

AUC	Area under the curve
CI	Confidence interval(s)
CRF	Case report Form
eCRF	Electronic Case Report Form
CTN	Clinical Trial Network
EPCO	European Perioperative Clinical Outcome definitions
ESAIC	European Society of Anaesthesiology and Intensive Care
EuSOS	European Surgical Outcome Study
ICH-GCP	International Council for Harmonisation - Good Clinical Practice
ICF	Informed Consent Form
ICU	Intensive care unit
IRB	Internal review board
NC	National Coordinator
OR	Odds ratio
PI	Principal Investigator
ROC	Receiver operating characteristics (curve)
RR	Relative risk
SAE	Serious adverse event
SOP	Standard operational procedure
SSC	Study steering committee
MAP	Mean Arterial Pressure



1. SPONSORSHIP AND GENERAL INFORMATION

1.1 Sponsorship

SQUEEZE is sponsored by a grant from the European Society of Anaesthesiology and Intensive Care Clinical Trial Network (ESAIC CTN). The aim of the European Society of Anaesthesiology and Intensive Care Clinical Trial Network is to provide an infrastructure for clinical research in the fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational European collaborative studies.

The Clinical Trial Network of the European Society of Anaesthesiology and Intensive Care can be contacted via:

Pierre Harlet, study coordinator

ESAIC Research Department

European Society of Anaesthesiology and Intensive Care

Rue des Comédiens 24

1000 Brussels, Belgium

Tel: +32 2 743 32 91

Fax: +32 2 743 32 98

E-mail: research@esaic.org ; squeeze@esaic.org

1.2 General Information

- Steering Committee

Dr. Ib Jammer, Haukeland University Hospital, Bergen, Norway.

Dr. Ben Creagh-Brown, Royal Surrey County Hospital, Guildford, United Kingdom.

Prof. Lui Forni, Royal Surrey County Hospital NHS Foundation Trust, Guildford, United Kingdom.

Dr. Hannah Wunsch, Sunnybrook Health Sciences Centre, Toronto, Canada.

Dr. Ramani Moonesinghe, University College London Hospitals, London, United Kingdom.

Dr. Anil Gupta, Karolinska University Hospital, Stockholm, Sweden.

- Statistician

Dr. Peter Martin, University College London Hospitals, London, United Kingdom.

2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The research project will be carried out in accordance with the research plan and the principles enunciated in the current version of the Declaration of Helsinki (amendment 2013) by the World Medical Association and the ICH-GCP Guidelines E6(R2). Specific national and local regulatory authority's requirements will be followed as applicable.

2.2 Risk categorisation

SQUEEZE is a prospective cohort study collecting clinical data on patients having non-cardiac surgery. No research-related interventions are anticipated, and all patients will receive routine care according to the standards laid out in each institution.

Some countries may choose to nest within this study additional assessments of patient outcome, or add biological sample collection or physiological assessments to add translational aspects – details of such studies will be provided outside this main protocol.

2.3 Institutional Review Board (IRB) or equivalent

In all cases, prior to study initiation, the local Principal Investigator (PI) at each centre must liaise with the national coordinator (NC) and ensure that they have taken the appropriate steps to seek authorization from relevant national/regional/local bodies to permit appropriate research study conduct. No substantial changes will be made to the protocol without prior IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

2.4 Participant Information and Informed Consent

There are three anticipated approaches:

1. This study may be considered to constitute research that requires individual patient consent.
2. In some countries it may be possible to successfully seek a waiver of individual patient consent from an appropriate regulatory authority - in the UK this is the Confidentiality Advisory Group (CAG) of the Health Research Authority (HRA).
3. In some countries it may be considered that, as there is no intervention and the data being collected is routine, and only fully pseudonymised data leaves the hospital, that this may be permissible without consent.

The SSC consider that the ideal approach is waived informed consent (2, above) because it minimises the risk of introducing selection bias. This approach was used in the UK national study SNAP-2 in 2017 as well as globally in the International Surgical Outcomes Study[1,2]. Patients at increased risk of receiving postoperative vasopressors are likely to be those who are more severely unwell, possibly with delirium,

possibly having emergency surgery – all conditions that predispose to difficulties obtaining informed consent. Therefore, by mandating individual informed consent we might systematically exclude patients of the greatest interest and consequently undermine the generalisability of our findings. Significant differences between participants and non-participants may threaten the validity of results from observational studies[3].

Consent procedures and provision of patient information will be conducted in accordance with local practice. If consent is required, it will be obtained as follows: prior to surgery, the patients will be presented with the IRB-approved ICF providing sufficient time and information for participant to make an informed decision about their participation in the study, i.e., explaining the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail.

In case of emergency surgery when there may not be enough time to collect consent or a patient may not be able to give consent, according to the Principal Investigator's judgement, consent may be obtained after surgery. In this case consent must be obtained within 7 days of surgery, or as deemed appropriate by Principal Investigator. Patients included in Cohort B can also give their consent after surgery; this is because it will not be known if a patient is eligible for the study until during surgery and at some sites it may not be possible to take consent from all patients undergoing surgery (especially as the percentage of eligible patients is expected to be small)

Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and without explanation, that withdrawal of consent will not affect his/her subsequent medical assistance and treatment and that no further data will be collected, while already collected, encoded data will be pseudonymised and analysis may be performed up to the point of data collection.

The participant will be informed that his/her medical records will be examined by authorised individuals other than their treating physician. The participant will read and consider the statement and will have the opportunity to ask questions before signing and dating the ICF, and will be given a copy of the signed document. Patients will confirm that they were given adequate time to reach a decision. The ICF must also be signed and dated by the investigator (or designee) and it will be retained as part of the study records.

The sponsor provides templates of Patient Information Sheet and Participant's ICF.

2.5 **Participant privacy**

The investigator affirms and upholds the principle of the participant's right to privacy and shall comply with applicable privacy laws. Specifically, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained because of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers and only pseudonymised data will be recorded in the central database.

For data verification purposes, authorised representatives of the sponsor or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.6 International considerations

This study will permit individuals from any country to express an interest in participation. Providing they can satisfy the SSC and ESAIC that they have the capacity to deliver the study in accordance with appropriate standards and sample a representative population from several hospitals within that country.

However, as this study is funded and supported by a European organisation the priority is to consider healthcare environments that are most similar Europe (acknowledging that within Europe there is a degree of variation). Patient data from patients in all countries within the Council of Europe (47 member states), Canada and USA, Australia and New Zealand will be analysed and reported in the main manuscript.

Information from other continents (Africa, Asia and South America) is no less valuable but will be reported separately to avoid considering incomparable healthcare environments together. For example, comparing patients enrolled in the African Surgical Outcomes Study (ASOS[4]) with those in the Europe Surgical Outcomes Study (EuSOS) demonstrates large differences.

Country level datasets will be compared and presented sensitively and with suitable emphasis on the inherent limitations of these comparisons including international differences in patterns of surgical disease and genetic backgrounds, as well as in healthcare systems. Comparisons will be made between countries grouped by income status (high/middle/low-income, according to worldbank.org) but we accept there are also significant limitations to this methodology.

If there is sufficient interest from a continent with an identified suitably experienced leader who wishes to coordinate activity in their region then the SSC and ESAIC will look upon this proposal favourably and this could result in a distinct analysis and manuscript.

2.7 Early termination of project

As an observational study, premature termination of the study resulting from ethical or safety concerns is exceedingly unlikely. In case of insufficient participant recruitment, the study period may be extended to reach the calculated sample size of 40,000 patients.

2.8 **Amendments, Changes**

Only the SSC or persons delegated by the SSC are entitled to amend the protocol. National Coordinators (NC) Local Principal Investigators (PI) will receive timely notification of changes and will be required to submit amendments locally. Written documentation of the amendments' approval will be provided to the sponsor and substantial amendments of the protocol will be only implemented after necessary local approvals. In consideration of the observational nature of the study, the necessity of protocol deviations to protect the rights, safety and well-being of human subjects without prior approval of the sponsor and the IRB appears remote. Such deviations must be documented and reported to the sponsor and the IRB as soon as possible.

3. INTRODUCTION

3.1 Background

Postoperative hypotension

Postoperative hypotension is a common occurrence following major non-cardiac surgery. Clinicians routinely evaluate patients to determine the cause(s) and start appropriate therapy. Postoperative hypotension is commonly due to a combination of decreased preload (typically due to relative hypovolaemia, potentially from bleeding or fluid redistribution) or decreased afterload. Less commonly there may be impaired cardiac contractility. Decreased afterload, otherwise known as vasodilatation, is commonly due to drug effects, neuraxial anaesthesia, or systemic inflammation, and it may be resistant to treatment or prolonged.[6]

Vasoplegia and vasopressor infusions

It is uncertain if vasoplegia best describes the extreme end of the spectrum of vasodilatation or is a pathophysiologically distinct entity representing uncontrolled failure of vascular homeostasis. Although most common after cardiac surgery, vasoplegia also occurs after major non-cardiac surgery, particularly when there has been significant bleeding and transfusion[6]. Cardiac output is not often measured postoperatively, but when measured, postoperative vasoplegia is characterised by low systemic vascular resistance, in the presence of a normal or raised cardiac output.

Once hypovolaemia has been excluded as a major contributing factor in hypotension, typically through administration of intravenous fluids, it is common to use vasopressor drugs (also known as vasoconstrictors) to counteract the vasodilatation. Intermittent dosing of short acting drugs ('bolus' therapy) has obvious disadvantages and therefore many clinicians use infusions of vasopressors.

Epidural anaesthesia is well recognised to cause vasodilation and this is commonly countered through the use of low-dose vasopressor infusions. Postoperative patients receiving higher doses of vasopressor infusions to maintain an adequate mean arterial pressure (MAP) can reasonably be described as experiencing postoperative vasoplegia. The main limitation to this is that exclusion of hypovolaemia is a prerequisite - but there is no absolute method to determine if this has been achieved. For the purposes of this study, receipt of infused vasopressors is considered as a surrogate indicator of significant vasodilatation. In some healthcare environments, the use of vasopressors in the postoperative period to support blood pressure following optimisation of fluid status is commonplace. The incidence of receipt of postoperative vasopressor infusions (PVI) has never been described.

3.2 Rationale for this study

There is evidence of substantial variation in the management of postoperative hypotension between centres, countries and continents. The variation is in assessment (cardiac output and invasive monitoring) and environment (post-operative care units, high-dependency units, ICUs) and management (use and choice of fluids and vasopressors/inotropes). We hypothesise that there is also variation in the incidence of organ dysfunction and the use of organ support, and in clinical outcomes including duration of stay and mortality.

In contrast to septic shock, there is no uniform definition of postoperative vasoplegia. Receipt of any amount of vasopressor would provide an objective dichotomous definition but a limitation would be the inability to differentiate degrees of vasodilatation. Use of a threshold dose of infused vasopressor to determine a definition is uncomfortably arbitrary.

There have been trials of different vasopressors to treat postoperative vasoplegia in cardiac surgical patients[7] and in the present study we intend to gather data to inform future trial design in noncardiac surgery.

3.3 Pilot data - 1

The European Surgical Outcomes Study (EuSOS) reported in the Lancet in 2012 in the publication entitled "Mortality after surgery in Europe: a 7 day cohort study"[5]. Data were collected on 46,539 patients, including 3599 who were treated postoperatively in a critical care unit. The Case Report Form included information about postoperative vasopressor (and inotrope) usage which has not been analysed or reported. With permission, we have performed a secondary analysis of these data and found: 2.7% of patients received either a vasopressor or inotrope within 24 hours of surgery; there was considerable variation between countries (from 0.0 to 6.3%); 75% of these patients were admitted to a critical care environment; and the most common vasoactive drug used was noradrenaline.

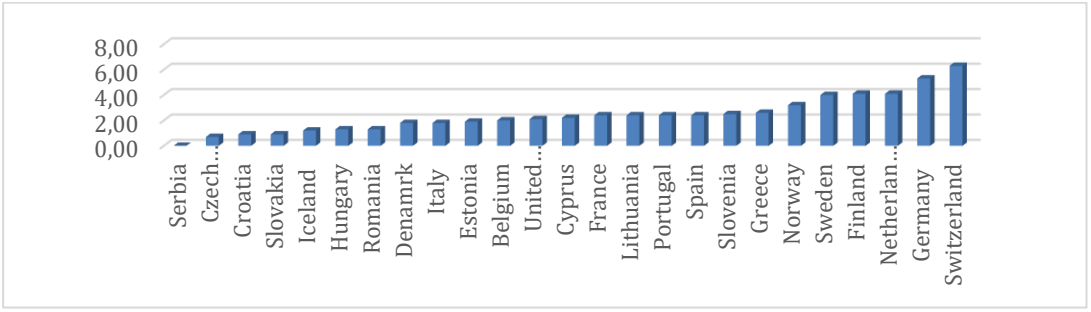


Figure 1: Unpublished secondary analysis of EuSOS data. Receipt of infused vasopressor or inotrope within 24 hours of surgery

3.4 Pilot data - 2

Between July 2018 and February 2019, we invited all members of ESAIC and ESICM respectively to participate in a 'micro-survey' that asked five very short questions. We received 2052 complete responses from 102 countries:

- Respondents indicated that 22% frequently, and 58% occasionally, encounter patients receiving postoperative vasopressor infusions. 20% of respondents considered it a rare event.
- The vasopressors used most often, in decreasing order of frequency, were noradrenaline/norepinephrine and phenylephrine.

4. RESEARCH QUESTIONS, OBJECTIVES

4.1 Definitions

Definition: Postoperative Vasopressor Infusion (PVI) is defined, for the purposes of this study, as the continuous intravenous infusion of a drug with a predominant vasoconstrictor effect (vasopressor). Therefore, repeated dosing of intravenous boluses is excluded, and infusion of a drug that is predominantly a positive inotrope (without concurrent vasopressor) is excluded. Additionally, we are not interested in vasopressor infusions that are used intra-operatively to counter the effect of general anaesthesia (or regional anaesthesia) and because this effect can take time to resolve, any infusion of vasopressor in the first hour following surgery is excluded – unless it continues after one hour following surgery. Infusions of vasopressor that are started more than 24 hours after the end of surgery is also excluded from this definition. Infusions of vasopressor that start before surgery will only be included if they also meet the above criteria.

Vasoactive drugs, grouped according to predominant action

Vasopressor	Not predominantly vasopressor
• Dopamine • Epinephrine (Adrenaline) • Metaraminol • Norepinephrine (Noradrenaline) • Phenylephrine • Vasopressin or Terlipressin • Akrinor® • Angiotensin II	• Atropine • Dobutamine • Ephedrine • Etilefrine • Glycopyrronnium • Nitrates • Milrinone

Table 1: Classification of vasoactive drugs. We accept that many drugs have mixed actions.

4.2 Research questions

- What proportion of patients receive PVI?
- Considering these patients:
    - What is the incidence of associated organ dysfunction; and what are their clinical outcomes?
    - Is there variation in incidence between different healthcare environments?
    - What factors (patient, condition, surgery, and intraoperative management), are associated with receipt of postoperative vasopressor infusions?
- In the management of patients with PVI following surgery, is there variation in practice between patients, hospitals and countries?
    - Are these variations in practice associated with clinical outcome?
- What is the health economic impact associated with postoperative vasopressor therapy?

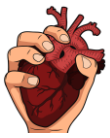
4.3 Aims (What we want to do)

- To determine characteristics associated with receipt of PVI – patient, condition, surgery, and intraoperative management.
- Characterise the variability within healthcare environments, between hospitals (not between practitioners) in usage of PVI.
- In patients receiving PVI, determine the dose and duration of therapy, and clinical outcomes.

5. PROJECT DESIGN

5.1 Type of research and general project design

SQUEEZE is a prospective, international, multicentre cohort study.



6. PROJECT POPULATION

We will recruit to two cohorts of patients.

6.1 Cohort A

Cohort A will include all patients admitted to participating hospitals during seven consecutive days with the following inclusion and exclusion criteria:

Inclusion criteria	Exclusion criteria
1. Undergoing surgery (may be planned or unplanned) 2. No plans for return home on the day of surgery. (No day case surgery) 3. Age ≥ 18 on day of surgery	1. Cardiac surgery 2. Obstetric surgery 3. Transplant surgery 4. Preoperatively long-term infusions of vasoactive drugs, such as epoprostenol (prostacyclin) 5. Mechanical circulatory support: ventricular assist device, intra-aortic balloon pump, artificial heart or similar 6. Already been enrolled in SQUEEZE

6.2 Cohort B

Cohort B will include 30 sequential patients with **a single additional inclusion** criterion:

Inclusion criteria	Exclusion criteria
1. Postoperative Vasopressor Infusion (PVI) – as defined above	1. Already been enrolled in SQUEEZE

6.3 Recruitment and Screening

Cohort A. Collecting consecutive data from all patients during a seven-day period will require significant human resources. Therefore, the PI will identify a suitably qualified team who are available on the preselected start time/date. Given the very broad entry criteria, most patients scheduled for surgery will be eligible. We anticipate that only a minority (<5%) of patients in cohort A will receive PVI.

Cohort B. PI and study team will actively look for patients who fulfil the criteria for cohort B (i.e., those receiving PVI). Depending upon local practice and case mix this could take months - maximum period of 12 months or until 30 patients are recruited, whichever occurs first. If centres wish to recruit more than 30 patients then will be permitted.

There is no rule on the order of the cohort that should start first. Centres can start recruiting to Cohort B and decide when to recruit Cohort A – as long as it is completed within 12 months after starting Cohort B recruitment.

Assessments

All patients will have data collected and entered into CRF1. Those patients who also receive PVI will have additional information collected and entered into CRF2. Every institution that intends to recruit patients in the study will complete an 'institutional survey' to allow characterisation of the healthcare environment.

Case Report Form 1 and 2 and included in the appendices. The CRFs will be transcribed into an electronic CRF (eCRF) hosted by ESAIC CTN.

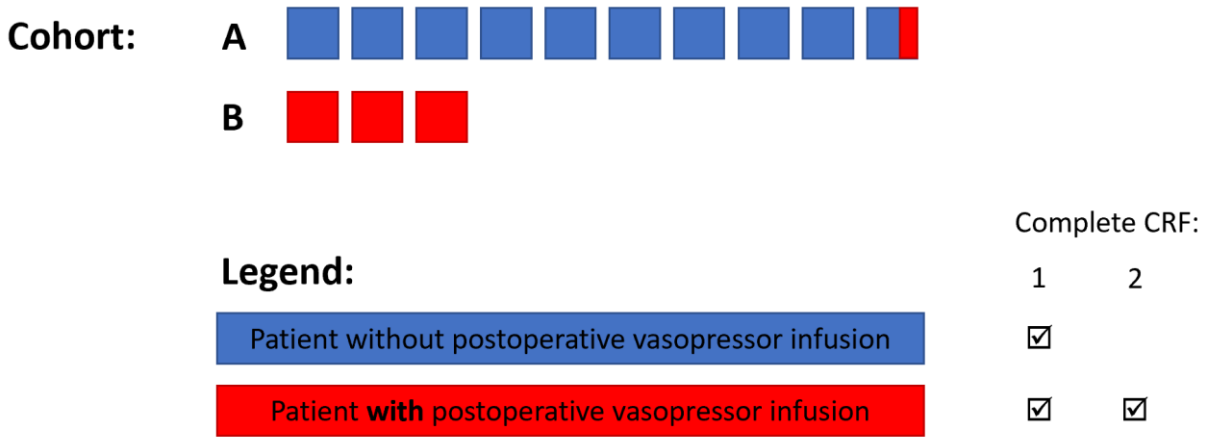


Figure 2: Difference between cohorts A and B, and CRF1 and 2

6.4 Assessments of primary endpoint outcome

Cohort A:

For cohort A the primary endpoint is the receipt of PVI.

Cohorts B (and those in Cohort A with PVI):

The primary endpoint will be death before discharge from the acute care hospital, censored at day 30.

6.5 Assessments of secondary endpoint/outcome(s)

For all patients, secondary outcomes include organ dysfunction, length of stay, and duration of critical care. These are recorded in CRF1.

Assessment of risk factors and other patient characteristics:

- Assessment of factors (patient, condition, surgery, anaesthesia) that potentially predispose to PVI – detailed in CRF1 in the appendix (all from A).
- Description of the population that receives vasopressors (some from A, all from B), detailed in CRF2 in the appendix. This includes the type of vasopressor used, the dose prescribed, and the duration of vasopressor use.

No additional testing, assessments, or evaluations will be conducted. These outcomes are purely ascertained from scrutiny of the medical records concerning events taking place during the index admission. As a pragmatic study we will be collecting outcome data prioritising ease of collection and being as objective as possible – for example although we would be interested in knowing the type of postoperative pulmonary complications, according to recent standardised endpoints in perioperative medicine definitions, or the EPCO definitions, it is easier for the local investigator to ascertain “invasive mechanical ventilation / NIV / both / neither”.

6.6 Data set

A realistic data set will be fundamental to the success of the investigation. We have identified the key data points whilst not discouraging centres from participating through an excessive burden of data collection. NC may request the addition of a limited number of data points to support the international SQUEEZE data collection and for subsequent national analyses. All additional data points must be discussed with the SSC.

Centre specific data will be collected once for each hospital including: Secondary/tertiary centre, Number of operating rooms, and number and level of critical care beds.

6.7 Assessment of optional endpoints

In some countries the NC will liaise with the SSC and it will be agreed that additional endpoints can be collected; a country-specific protocol will be written. For example, in the UK we will have the additional endpoints of:

- Long-term mortality: Vital status up to 5-years following surgery, from NHS central database.

6.8 Translational studies

Similarly, we encourage NCs to consider adding biological sample collection, or physiological assessments to one or more recruiting centres in their country. The SSC will consider all requests and potentially support applications for additional funds to facilitate the delivery of such studies.

Local or national cohorts addressing additional questions and collecting additional data while sharing part of the variables collected for SQUEEZE, are allowed under the following conditions: nomination of a separate sponsor (i.e., other than the ESAIC), separate ethical approval, separate informed consent, independent data management, and approval of a detailed study proposal by the SSC. The Sponsor and the SSC have the right to veto the nesting of a study. For transparency, the original paper should be referenced in all articles of additional analyses. Authorship rules for potential publications derived from such additional cohort studies are to be submitted to the Sponsor and SSC together with the study proposal.

6.9 Methods of minimising bias

Selection bias will be limited through waived consent processes where applicable and the short period of data collection for Cohort A, which is designed to enable participating hospitals to collect data on all of their eligible patients within the data collection week, which has a good chance to result in a representative sample. Information bias will be limited through use of a robust case report forum with clearly specified definitions. A pre-specified statistical analysis plan will ensure that Type 1 error inflation through multiple hypothesis tests is minimised and controlled.

7. LOGISTICS OF DELIVERY

7.1 Study centres and role of national coordinators (NC) and local principal investigators (PI)

We aim to recruit as many centres from high- and middle-income countries as possible. We aim to have at least 20 countries. Within each country, we will aim to recruit as many centres as possible. The number of centres will inevitably vary by country. The NC will scrutinise potential participating hospitals to ensure that they will be able to collect the necessary data - guidance will be provided. Each centre should recruit consecutive data from all patients during a seven-day period, followed by 30 subsequent patients that receive postoperative vasopressors. See chapter 5.1. and 5.2 for inclusion/exclusion criteria. Recruiting from low-income countries has previously been found to be challenging due to resource constraints[4] but they will not be excluded from participating.

We aim to meet or exceed this target through the activities of national lead investigators and the support of key organisations such as the European Society of Anaesthesiology and Intensive Care and other supporting societies (ESICM).

Centres

Study centre registration occurs online via the dedicated "Call for Centres form" on the ESAIC website. Within the period of recruitment planned for SQUEEZE, the start of recruitment for individual centres (12 months) is at the discretion of the local PI. Recruitment will continue until each centre has recruited all eligible patients for one week plus an additional 30 patients that receive vasopressors or 12 months have passed since starting to recruit cohort B.

National coordinators

National coordinating investigators are appointed by ESAIC and the SSC to lead the project within individual countries and their responsibility includes:

- Identify participating centres in their country and recruit local PIs in participating hospitals;
- Assist in the translation of study documents;
- Ensure that all necessary national or regional regulatory approvals are in place prior to start of patient inclusion;
- Assist and train the Local PI and monitor the conduct of the study according to GCP;
- Ensure good communication with ESAIC headquarters and the participating sites in his/her countries during all study steps including data cleaning.

Principal investigators

Local PI are specialists working in perioperative medicine in each participating institution who will have the following responsibilities:

- Provide leadership for the study in their institution;
- Ensure all relevant regulatory/ethical approvals are in place for their institution;

- Ensure adequate training of all relevant staff prior to data collection;
- Supervise enrolment, daily data collection, and assist with problem solving;
- Adjudicate events
- Ensure timely completion of eCRF, follow-up assessments, and data cleaning queries. The Local PI is the main responsible for ensuring integrity of data collection. By signing the data on eCRF Local PI confirms the data integrity´;
- Communicate with ESAIC headquarter and the relevant National Coordinating Investigator during all study steps including data cleaning.

7.2 Milestones and planned timelines

		2019				2020				2021				2022				2023
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	All year
1	Protocol and CRF																	
	National co-ordinators																	
2	National ethics and governance																	
3	Recruitment																	
4	Data cleaning																	
	Analysis and write-up																	
	Outputs																	

7.3 Assessment of safety and reporting

As a fully observational study that has no additional assessments there is no risk of study participation contributing towards any adverse events. Therefore, there will be no reporting of adverse events.

7.4 Determination of Sample Size

We aspire to collect data from at least 400 hospitals and expect that the average number of patients recruited for cohort A will be about 100 patients. Thus, we expect to collect data for 40,000 patients in Cohort A. Our secondary analysis of EuSOS (unpublished) showed an average use of vasoactive drugs of 2.7%. Assuming that a lesser proportion of these drugs were inotropes, we estimate 2% vasopressor usage. Based on this estimate, we anticipate that around 800 patients (95 % CI: between 745 and 855 patients, assuming a binomial distribution) will receive PVI. We expect to have a sufficient number of events for exploratory analyses investigating several potential risk factors of vasopressor use and their potential interactions.

For cohort B, we estimate a sample of 12,000 patients (30 patients from each of 400 hospitals). Thus, we expect our total sample of patients with PVI to be around 12,800 patients (12,000 from cohort B plus 800 who were in cohort A but also received PVI and had CRF2 completed). This should be an adequate sample to provide robust estimates of duration of vasopressor use and allow for exploratory analyses around timing of cessation and associated outcomes.

7.5 Planned analyses

7.5.1 Main analyses

A detailed statistical analysis plan will be written and published prior to completion of database closure. This is an exploratory study of a large data set based on a self-selected set of hospitals. Although our sampling procedures give us a good chance of achieving a representative sample of patients within each participating site, we do not claim to be able to achieve a random sample of hospitals from participating countries, or a representative sample of patients for any country as a whole. Thus, thorough description and graphical representation of the data will be important methods of analysis, and often take precedence over inferential procedures. Some statistical models will be employed to aid description and estimation of essential parameters, as outlined below. We will summarize patient characteristics using means, standard deviations, medians, interquartile ranges, and percentages as appropriate.

For cohort A we will summarize the primary endpoint as a percentage of patients who receive PVI. We will also describe the variation in PVI use between hospitals and countries. Mixed effects logistic regression will be used to document this variation employing a shrinkage estimator (best linear unbiased prediction) to control for regression to the mean, and caterpillar plots.

Using patients from both Cohorts A and B, we will assess the relationship between PVI and potential risk factors using bivariate odds ratios. We will use multivariate mixed effects regression with a set of

plausible predictor variables to assess which are most strongly associated with receipt of PVI. A shrinkage method (penalized regression, such as lasso) will be applied to the regression model in order to reduce the type 1 error rate and reduce the risk of inflated estimates of strength of associations.

Using patients from both Cohorts A & B, we will assess the relationship between PVI and in-hospital mortality as well as secondary outcomes, using logistic regression and other statistical models as appropriate. Once again, we will use a shrinkage method to avoid overfitting. We will also describe variation in these outcomes between hospitals and countries.

Using patients from both Cohorts A & B, we will graph duration of vasopressor use using Kaplan-Meier curves and assess for any clear cut-offs to create a definition of prolonged vasopressor use. We will assess the relationship between patient characteristics (including co-morbidities) and duration of vasopressor use using survival analysis. We will summarize the frequency of organ dysfunction based on different durations of post-operative vasopressor use and associated mortality. The purpose of these analyses is to document observed associations to inform future randomised trials that may wish to assess the effect of vasopressor use on outcomes.

7.5.2 Identifying sub-cohorts

Before the start of data collection, we will conduct an expert review to ascertain, in advance of seeing the data, plausible subgroups for stratified analysis. For example, we may wish to analyse separately patients who receive emergency surgery for sepsis. Details of these planned analyses will be specified in the study protocol to be submitted for publication.

7.5.3 Handling of missing data or inadequate patient recruitment

We will exclude patients from either cohort if the data is of insufficient quality, or completeness. Similarly, we will exclude centres (and all the patient data from those centres) if the number of patients recruited is insufficient. Proportions of missing values will be documented for each variable individually and for the data set as a whole. We will examine the need for and appropriateness of multiple imputation of other missing data based on the final data collected and based on an assessment of the likely processes that caused observation to be missing.

8. DATA AND QUALITY MANAGEMENT

8.1 Data quality

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control measures will be applied to each stage of data handling to ensure that

all data are reliable and have been processed correctly, including written SOP (in English for all countries) for data collection and entry, automated consistency checks, and training of NC and local PI. It will be responsibility of the NC, with support by the study coordinating office, to train local PI. Local PI will ensure that the data in the eCRF is carefully entered and verified regularly. It will be the responsibility of local PIs to conduct periodic and random checks to ensure data quality in her/his centre. The sponsor will make random assessments of centres to confirm that there is no improper and incorrect data entered into the eCRF. On-site monitoring visits by the sponsor are not planned.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Any agreements, made by the sponsor with the investigator/institution and any other parties involved with the study, will be in writing, as part of the protocol or in a separate agreement. No fee or financial compensation is given to PI and/or participating institution for patient recruitment

8.2 Data handling and record keeping / archiving

Data will be entered into a secure on-line database protected by personalised and confidential usernames and passwords and documenting the time and individual entering the data. The language of the online database, eCRF, and the relative SOPs is English and will not be translated in the national languages. Data will be collected directly from source documents into the encoded paper CRF and secondarily entered into the eCRF. A copy of the original source documents will be stored within a locked cabinet/office accessible to authorised personnel only in accordance with local and national regulations. An identifiable patient data page reporting the assigned patient identification code will be stored separately also in a locked cabinet/office (accessible to authorised personnel only) to record in-hospital outcomes, supply missing data points, and to allow potential monitoring visits by National Coordinating Investigators, Sponsor, IRB, or regulatory authorities. Signed ICF to document that written informed consent was obtained will be stored as described above. All study documents will be archived as required by local legislation.

Sponsor and centres will maintain and update their trial master files according to the recommendation of the ICH-GCP Guidelines E6(R2). All collected data will remain the property of the Sponsor.

8.3 Confidentiality, Data Protection

To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification code and identifiable patient data will be stored separately in a locked cabinet accessible to authorised personnel only and corresponding electronic

files will be protected by personalised and confidential usernames and passwords. eCRF are identified through the patient identification code and will not include any names, initials, date of birth or local hospital patient numbers; therefore, no patient identifiable data will be directly accessible from the eCRF. Data protection will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Further, only encrypted data will be stored centrally. The database will be hosted on servers physically located in the European Union and data can only be transferred to servers located in member States of the European Union or in other countries where the level of personal data protection has been determined as adequate by the European Commission on the basis of the General Data Protection Regulation (GDPR, Article 45).
Open direct access to all relevant study information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections to the sponsor, national coordinators, IRB, or regulatory authorities. All handling of personal data will comply with the GCP Guidelines and follow strictly the legal and national requirements of GDPR. For any additional question please contact the ESAIC Data Protection Officer at privacy@esaic.org or 24, Rue des comédiens 1000 Brussels, Belgium.

SQUEEZE Appendix 7 - Data Protection Overview is destined to any person involved in the SQUEEZE study to have a better understanding of the data flow and data storage of the study.

SQUEEZE Appendix 10 – Lawfulness of processing of data – GDPR can be used to give an overview to the patients of the processing of the patient's data. The first part of the document details the information that can be given to the patient while the second part explains the situation to the Local Investigator.

9. PUBLICATION AND DISSEMINATION POLICY

9.1 Publication of results

The main results of SQUEEZE and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia and national meetings.

As recommended by the International Committee of Medical Journal Editors, authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, and submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Members of the SSC and other particularly committed investigators (see below) that fulfil those criteria will be part of the Writing Group. The members of the Writing group and the "SQUEEZE Investigators" will be authors of the publications derived from SQUEEZE. When submitting a manuscript, the corresponding author will specify the group name as "SQUEEZE Investigators". According to the recommendations issued by the International Committee of Medical Journal Editors, the by-line of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors and collaborators whichever names appear on the by-line. To ensure that MEDLINE will list the names of individual group members who are collaborators, there will be a note associated with the by-line clearly stating that the individual names are elsewhere in the paper and that those names are collaborators. The local PI will be asked to submit names of staff actively involved from their institution in the End of Study Reporting Form.

Presentation at international meetings will be restricted to the members of the SSC or their delegates. National Coordinators will qualify for presentation at national meetings after approval by the SC and the sponsor. ESAIC Clinical Trial Network will be acknowledged in all publications and presentations.

9.2 Secondary analyses, and data sharing

After publication of the pooled results, centres will be allowed to use their own data for local presentation and publication. Duplicate data publication is not permitted.

The pseudonymised pooled dataset may be available for secondary analyses upon specific request in form of a detailed study proposal (including authorship rules) to the SSC. Only collaborators may have access to the study data. The final approval of these potential secondary analyses rests with the SC. Prior to journal submission, any paper originating from the pooled data will be reviewed by the SC that is also entitled to require revisions. Authorship of any publication derived from the pooled data set will include the group name "SQUEEZE Investigators" with a by-line clearly stating that the individual

names are elsewhere in the paper. For transparency, the original paper has to be referenced to in all articles of secondary analyses.

Requests for data sharing for individual-level meta-analyses are to be addressed to the Sponsor and SC.

The sponsor of the study (ESAIC CTN) can use pseudonymised pooled data for internal analyses and educational purposes.

10. FUNDING AND SUPPORT

SQUEEZE is sponsored by a grant from the European Society of Anaesthesiology and Intensive Care Clinical Trial Network (ESAIC CTN). The submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the sponsor and the SSC. The SSC members declare not to have any conflicts of interest (a declaration of conflict of interest will be signed by each SC member and kept by the Sponsor).

11. INSURANCE

SQUEEZE is a minimal-risk, observational study. Insurance might be required based upon individual agreement between local Principal Investigator and the relevant institutional legal department. The ESAIC has Public Liability insurance in place to cover the legal liability of the ESAIC as Sponsor in the eventuality of harm to a research participant arising from management of the research by the ESAIC. This does not in any way affect the responsibility of a Centre for any clinical negligence on the part of its staff.

12. REFERENCES

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13. LIST OF APPENDICES

1A – Patient Information Sheet

1AB – Patient Information Sheet and Consent Participation Form

2 – Case Report Form

3 – Pre-Study Survey

4 – Approval Documentation Coversheet

5 – Confidential Patient Logsheet

6 – End of Study Reporting Form

7 – Data Protection Overview

8 – Authorship policy

9 – Protocol Synopsis

10 – GDPR - Lawfulness of processing

11 – National Coordinators List

14. PROTOCOL CHANGES HISTORY

Version Number	Change #	Page	Section	Description of changes
1.12	**1**	**3**	**Protocol Signature Sheet**	"Name, Date and Signature" under each label **Changed to** "Name, Date and Signature" under the first label "Co-Chief Investigators".
1.12	**2**	**3**	**Protocol Signature Sheet**	"Local Principal Investigators (enter local details, as applicable)" label created, and spaces for "Name, Date and Signature" to be written added.
1.12	**3**	**32,33**	**List of Appendices**	"List of Appendices" section created, including : 1A – Patient Information Sheet 1AB – Patient Information Sheet and Consent Participation Form 2 – Case Report Form 3 – Pre-Study Survey 4 – Approval Documentation Coversheet 5 – Confidential Patient Logsheet 6 – End of Study Reporting Form 7 – Data Protection Overview 8 – Authorship policy 9 – Protocol Synopsis 10 – GDPR - Lawfulness of processing 11 – National Coordinators List
1.12	**4**	**33, 34**	**Protocol Changes History**	"Protocol Changes History" section added.
1.12	**5**	**3**	**Protocol Signature Sheet**	Dates and signatures added for the Co-Chief Investigators
1.12	**6**	**3**	**Protocol Signature Sheet**	Steering Committee and Statistician boxes removed.
1.12	**7**	**9**	**Sponsorship and General Information**	"1. Sponsorship" changed to "1. Sponsorship and General Information"
1.12	**8**	**9**	**Sponsorship and General Information**	Labels "1.1 Sponsorship" and "1.2 General Information" added.
1.12	**9**	**9**	**Sponsorship and General Information**	Steering Committee members and statistician added in "1.2 General Information" : 1.2 General Information • Steering Committee

				Dr. Ib Jammer, Haukeland University Hospital, Bergen, Norway. Dr. Ben Creagh-Brown, Royal Surrey County Hospital, Guildford, United Kingdom. Prof. Lui Forni, Royal Surrey County Hospital NHS Foundation Trust, Guildford, United Kingdom. Dr. Hannah Wunsch, Sunnybrook Health Sciences Centre, Toronto, Canada. Dr. Ramani Moonesinghe, University College London Hospitals, London, United Kingdom. Dr. Anil Gupta, Karolinska University Hospital, Stockholm, Sweden. • Statistician Dr. Peter Martin, University College London Hospitals, London, United Kingdom.
1.12	**10**	**6,7**	**Summary**	**CTGOV ID added : NCT03805230**
1.12	**11**	**5, 6**	**Contents**	**Table of Contents updated**
1.12	**12**	**29**	**Confdentiality, data protection**	This was added "SQUEEZE Appendix 7 - Data Protection Overview is destined to any person involved in the SQUEEZE study to have a better understanding of the data flow and data storage of the study. SQUEEZE Appendix 10 – Lawfulness of processing of data – GDPR can be used to give an overview to the patients of the processing of the patient's data. The first part of the document details the information that can be given to the patient while the second part explains the situation to the Local Investigator."
2.0	**1**	**1**	**Sponsor/funder**	"European Society of Anaesthesiology" changed to "European Society of Anaesthesiology and Intensive Care" and "ESA" changed to "ESAIC" throughout all document to reflect society name change
2.0	**2**	**1**	**Study Identifier**	**Squeeze changed to SQUEEZE throughout all documents**
2.0	**3**	**7**	**Protocol synopsis**	**Project Duration, Schedule :** "From spring 2020: Start inclusion of patients for cohort A and B. From spring 2021: Data analysis and writing manuscript End of 2021: Submission of primary research paper." **Changed to** "From Autumn 2020: Start inclusion of patients for cohort A and B. From 2022 : Data analysis and writing manuscript 2023 Submission of primary research paper."

2.0	**4**	**11**	**Participant Information and Informed Consent**	"Consent procedures and provision of patient information will be conducted in accordance with local practice. If applicable (1, above), patients' consent will be sought as follows: prior to surgery, the patients will be presented with the IRB-approved ICF providing sufficient time and information for participant to make an informed decision about their participation in the study, i.e., explaining the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail." **Changed to :** "If consent is required, it will be obtained as follows: prior to surgery, the patients will be presented with the IRB-approved ICF providing sufficient time and information for participant to make an informed decision about their participation in the study, i.e., explaining the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail. In case of emergency surgery when there may not be enough time to collect consent or a patient may not be able to give consent, according to the Principal Investigator's judgement, consent may be obtained after surgery. In this case consent must be obtained within 7 days of surgery, or as deemed appropriate by Principal Investigator. . Patients included in Cohort B can also give their consent after surgery; this is because it will not be known if a patient is eligible for the study until during surgery and at some sites it may not be possible to take consent from all patients undergoing surgery (especially as the percentage of eligible patients is expected to be small)"
2.0	**5**	**19**	**Project Population-Cohort B**	**"**Already been enrolled in SQUEEZE" **added as exclusion criteria**
2.0	**6**	**20**	**Recruiting and Screening**	B. Following completion of recruitment to cohort A, the study will remain open and screening should continue – actively looking for patients who fulfil the criteria for cohort B (i.e., those receiving PVI). Depending upon local practice and case mix this could take months - maximum period of 12 months or until 30 patients are recruited, whichever occurs first. If centres wish to recruit more than 30 patients then will be permitted." **Changed to :** Cohort B. PI and study team will actively look for patients who fulfil the criteria for cohort B (i.e., those receiving PVI). Depending upon local practice and case mix this could take

				months - maximum period of 12 months or until 30 patients are recruited, whichever occurs first. If centres wish to recruit more than 30 patients then will be permitted. There is no rule on the order of the cohort that should start first. Centres can start recruiting to Cohort B and decide when to recruit Cohort A – as long as it is completed within 12 months after starting Cohort B recruitment."
2.0	**7**	**25**	**Milestones and planned timelines**	**Table is updated according to new timeline.**
2.0	**8**	**28**	**Data handling and record keeping/archiving**	Signed ICF to document that written informed consent was obtained prior to enrolment will be stored as described above. **Changed to:** "Signed ICF to document that written informed consent was obtained will be stored as described above." **"**All collected data will remain the property of the Sponsor**" is added.**