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Stepped wedge cluster randomised controlled trial to assess the effectiveness of an optimisation strategy for general anaesthesia on postoperative morbidity and mortality in elderly patients (the OPTI-AGED study): a study protocol

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ABSTRACT

Introduction Elderly patients constitute an increasingly large proportion of the high-risk surgical group. In adult patients, several specific intraoperative approaches such as cardiac output-guided haemodynamic therapy, depth of anaesthesia monitoring (DAM) or lung-protective ventilation (LPV) are designed to reduce postoperative mortality and surgical complications. However, none of these approaches has been specifically performed in the elderly, and no evaluation of a multimodal optimisation strategy for general anaesthesia has been achieved in this population.

Aims The objective of this study is to assess, in high-risk patients aged 75 years and over undergoing high-risk surgery, the effectiveness of combined optimisation of anaesthesia involving goal-directed haemodynamic therapy (GDHT), LPV and electroencephalographic DAM on postoperative morbidity and mortality. The primary outcome of the study is a composite criterion associating major postoperative complications and mortality occurring within the 30 first postoperative days. The secondary outcomes are 1-year postoperative autonomy and mortality.

Methods and analysis This prospective, randomised, controlled, multicentre trial using a stepped wedge cluster design will be conducted in 27 French university centres. Patients aged 75 years and over, undergoing femoral head fractures and major intraperitoneal or vascular elective surgeries will be included after informed consent. They will benefit from usual care in the 'control group' and from a combined optimisation of general anaesthesia involving GDHT, LPV and DAM in the 'optimisation group'. The cluster's crossover will be unidirectional, from control to optimisation, and randomised. Data will be recorded at inclusion, the day of surgery, 7 days, 30 days and 1year postoperatively and collected into a hosted electronic case report form. The primary outcome of the study is a composite criterion associating major postoperative complications and mortality occurring within the 30 first postoperative days. The secondary outcomes are 1- year postoperative autonomy and mortality.

Ethics and dissemination This protocol was approved by the ethics committee Sud-Est 1 and the French regulatory agency. The finding of the trial will be disseminated through peer-reviewed journals and conferences

Trial registration number NCT02668250; Pre-results.

Strengths and limitations of this study

- The optimisation of general anaesthesia in aged (OPTI-AGED) trial is the first large study designed to investigate in elderly patients the effectiveness of a multifaceted optimisation of general anaesthesia involving haemodynamic intervention, lung-protective ventilation and electroencephalographic monitoring of anaesthesia depth.
- Major morbidities and mortality will be assessed at postoperative day 30, as well as long-term (1 year) patient's autonomy and mortality.
- A stepped wedge design will be used involving sequential roll-out of the intervention to clusters of participant centres.
- As in a stepped wedge design, more clusters are exposed to the intervention towards the end of the study than in its early stages, the effect of the intervention might be confounded with any underlying temporal trend.
- The unblinded design of the study may lead to a contamination bias during the control period where investigators may seek to improve their performance and to an information bias related to physicians assessing outcomes by knowing the time period of the study.

INTRODUCTION

Elderly patients: an increasing and a high-risk surgical group

As the population is expanding and ageing, the number of patients aged 75 years and over undergoing surgery is rising[1] and constitute an increasingly large proportion of the high-risk surgical group. More than 2/3 of postoperative deaths in UK concern patients of more than 70 years old.[2] Cardiac and pulmonary postoperative complications are equally prevalent[3 4] in this population and affect morbidity, mortality and length of hospital stay.[5] Comorbidities and surgical pathologies by themselves[6] are determinants of postoperative morbidity and mortality in elderly.

Anaesthetic optimisation of high-risk surgical patients

Flow monitoring and haemodynamic optimisation

In high-risk patients undergoing surgery, meta-analyses have suggested that goal-directed haemodynamic therapy (GDHT) significantly reduced mortality and surgical complications.[7 8] The volume of available evidence led the National Institute of Health and Care Excellence, the UK National Health Service[9 10] and the Société Française d'Anesthésie et de Réanimation[11] to endorse in their respective recommendations the use of haemodynamic optimisation algorithms for the perioperative care of high-risk surgical patients. Even if recent evidence suggests that GDHT is not bringing the added benefit to the care of surgical patients that was previously described,[12–14] it may only mean that focusing solely on haemodynamics is a too simplistic approach. Haemodynamic optimisation and GDHT have to be considered mainly as part of a bundle of treatments that encompasses all facets of care for these patients.[15]

Lung-protective ventilation (LPV)

In a recent and large sample-sized study, the use of a LPV strategy (with tidal volume of 6–8 mL per kilogram of predicted body weight (PBW), positive end-expiratory pressure (PEEP) of 6–8 cm of water and recruitment manoeuvres repeated every 30 min after tracheal intubation) in intermediate-risk and high-risk surgical patients undergoing major abdominal surgery was associated with improved clinical outcomes when compared with a practice of non-protective mechanical ventilation.[16]

Depth of anaesthesia monitoring (DAM)

Several observational studies[17–24] reported an association of cumulative duration of deep anaesthesia (measured by a bispectral electroencephalographic (EEG) index value (BIS) below 40–45) with intermediate-term mortality after surgery. This association is not necessarily causal and may be an epiphenomenon, low-processed EEG index values being a marker of a significant frailty associated with an increased risk of early death. However, excessive deep anaesthesia and coincident hypotension were strongly associated with poor outcomes in a large cohort of 2662 patients.[23] In a recent study using EEG burst suppression for more than 5 min as a definition of deep anaesthesia, the combination of burst suppression and low mean arterial blood pressure was strongly prognosis of poor outcomes .[24] Monitoring depth of anaesthesia by processed EEG indices decreased the rate of postoperative delirium in patients aged 60 years or older in three randomised studies.[25–27] This may be caused by reducing states of deep anaesthesia evidenced by extremely low BIS values or by reducing unnecessary increases in anaesthetic administration.[25 26] The association of deep anaesthesia and poor postoperative outcome suggests that BIS monitoring could reduce the incidence of unfavourable outcomes.[28]

There is an increasing knowledge that intraoperative care may contribute to postoperative adverse outcomes, but none of the published studies performed a specific analysis in elderly patient's population. Moreover, to our knowledge, there is no study in the literature evaluating the benefit of a multifaceted strategy of general anaesthesia optimisation.

Hypotheses and aims

It is hypothesised that combining these different approaches to optimise general anaesthesia could maintain or increase oxygen delivery, eliminate intraoperative oxygen debt and improve postoperative outcomes.

In elderly patients, who represent a particularly vulnerable population of patients, this trial aims to test the effectiveness of a multifaceted strategy of general anaesthesia optimisation based on GDHT, DAM and prophylactic LPV, to reduce postoperative major morbidity and mortality occurring within the 30-day postoperative period. The secondary objective of the trial is to evaluate long-term patient's outcomes measured by 1-year postoperative autonomy and mortality.

METHODS AND ANALYSIS

Ethics

Written consent will be obtained from all participants. The study was registered by the French regulatory agency (Agence National de Sécurité du Médicament et des produits de santé (ANSM) on 17 June 2016 with registration number IDRCB: 2016-A00667-44 and was also registered on the ClinicalTrials.gov website on 27 June 2016 with trial identification number NCT02668250 (Pre-results). The study will be conducted in accordance with the current revision of the Declaration of Helsinski, 1996,[29] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and the applicable French regulatory requirements.

Trial design

The present study will use a stepped wedge, cluster randomised controlled design conducted in 27 French university centres (online supplementary appendix 1). This design was chosen because the interventions to optimise general anaesthesia involve changing

Table 1 Stepped wedge study design of OPTI-AGED trial

	Initiation	Step1	Step2	Step3	Step4	Step5
Cluster 1	Control	Control	Control	Control	Control	Intervention
Cluster 2	Control	Control	Control	Control	Intervention	Intervention
Cluster 3	Control	Control	Control	Intervention	Intervention	Intervention
Cluster 4	Control	Control	Intervention	Intervention	Intervention	Intervention
Cluster 5	Control	Intervention	Intervention	Intervention	Intervention	Intervention

Six intervals of 4 months will be fixed over 24 months.
The randomisation will involve five steps for which 5–6 centres will be included in each cluster.

of physician practice. A simple randomised trial would require the physicians to ignore the intervention's principles and skills they have learnt when treating patients, making the likelihood for contamination very high. Each of the different interventions proposed in the study is likely to do more good than harm, so it may be considered as unethical to withhold an intervention anticipated to be beneficial from a proportion of participants. Thus, a cluster randomised controlled trial using a parallel group design in which the clusters are randomised to either the interventions or the control arm of the study was considered to be not suited to our study. These elements argue for employing a stepped wedge design. A stepped wedge cluster randomised controlled design allows to sequentially deliver the interventions to all trial clusters over a number of time period (table 1). The order in which the clusters receive interventions is randomised, and by the end of the study, all clusters will have adopted the interventions.

The Consolidated Standards of Reporting Trials (CONSORT) diagram of OPTI-AGED is presented in figure 1.

Randomisation

Centres will be randomly allocated to a cluster by the study's statistician using random blocks randomisation sequence generated in Stata software (V.13). The cluster constitution was stratified according to planned recruitment of each participant centre for each type of surgery involved in the study. A cluster regrouping 5–6 centres will be the unit of randomisation. Considering the number of participating centres (n=27) and the duration of this study (24 months), it was proposed a sequential roll-out of the intervention to the clusters involving five steps over six time periods. The order in which clusters receive the intervention is determined at random.

Selection of participants

Patients will be included in the OPTI-AGED trial if they comply with the indicated inclusion and exclusion criteria.

Inclusion criteria

For inclusion, patients aged 75 years and over must meet all the following criteria:

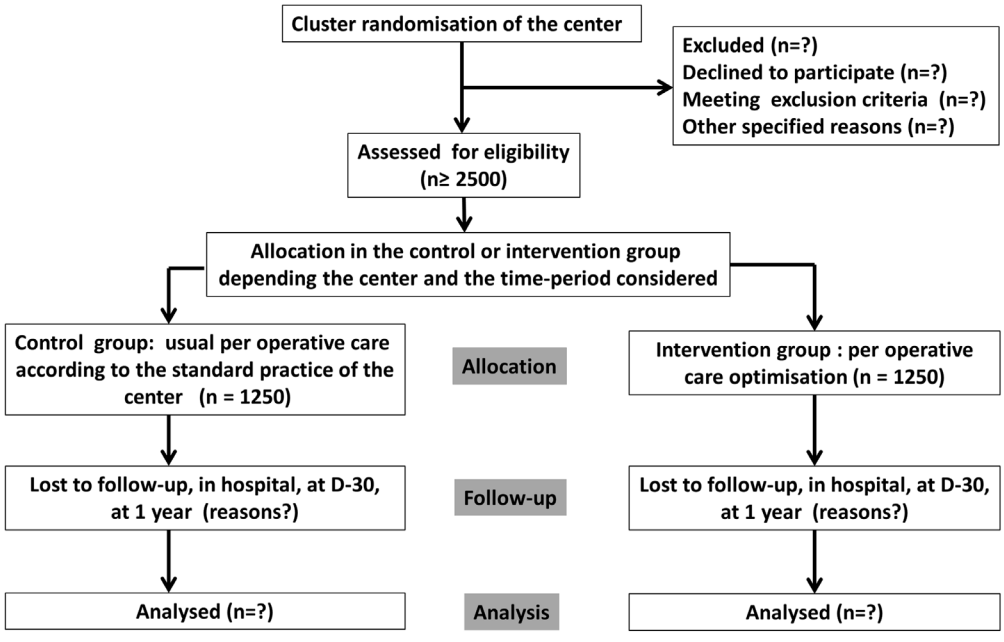

Figure 1 CONSORT flow chart illustrating the randomisation and flow of patients in the study. CONSORT, Consolidated Standards of Reporting Trials.

1. Elective or emergency surgeries including femoral head fracture, major intraperitoneal abdominal surgery lasting >90 min (excluding cholecystectomy and abdominal wall surgery) and vascular surgery (excluding venous surgery and arteriovenous fistula surgery) under general anaesthesia.
2. At least one of the following comorbidities: ischaemic coronary disease; cardiac arrhythmia; congestive heart failure; peripheral vascular disease; dementia; stroke; chronic obstructive pulmonary disease; chronic respiratory failure; chronic alcohol abuse; diabetes; chronic renal failure; and active cancer.
3. From whom written informed consent is obtainable either from the patient or from a patient's legal representative.
4. Who is affiliated to French Assurance System.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

1. Patient with acute heart failure and acute coronary syndrome.
2. Patient with acute respiratory failure or pneumonia.
3. Patient with preoperative septic shock.
4. Patient with acute stroke.
5. Patient with evolutive neuromuscular disorder.
6. Thoracic surgery or combined abdominal and thoracic surgery.

Local physicians will introduce the trial to patients or to a legally authorised representative in case of lack decisional capacity of patient due to mental status. Individual's decisional capacity will be determined by the investigating physician in agreement with the family without the use of a formal capacity instrument. Information sheets and consent forms are provided for patients or their legally authorised representative by the physician (see online supplementary appendices 2 and 3). If inclusion was performed after proxy consent was obtained from a legally authorised representative, informed agreement of the patient to continue participation will be solicited if he regains decisional capacity postoperatively.

Trial interventions

All included patients will be allocated to one of the following two study groups depending on the inclusion cluster of the centre and the time period considered (compared with table 1 and figure 1).

Both the control group and the intervention group will undergo general anaesthesia by intravenous induction and maintenance by intravenous or halogenated agent associated with an opioid agent and a muscle relaxant when required by surgery or considered useful by the anaesthetist.

All treatment decisions except optimisation measures will be at the discretion of and undertaken by senior anaesthetists. Nevertheless, investigators will be strongly encouraged to apply standard measures to avoid extremes of clinical practice as follow:

1. Appropriate prophylactics antibiotics will be used as recommended.
2. Blood products will be given to maintain haemoglobin at level greater then 8 g/dL or 10 g/dL in case of ischaemic heart disease.
3. Postoperative pain management in order to achieve a visual analogue scale pain score of <30/100 using either locoregional analgesia or patient-controlled intravenous morphine.

Control group

Patients will receive usual peroperative care according to the standard clinical practice of the anaesthesia department considered concerning DAM, protective ventilation, GDHT and hypotension treatment. It will be determined in each centre with the staff concerned and formalised as such before starting patient's inclusion. This standard of care will be applied to all the patients of the same centre during the control period.

Intervention group

Patients will benefit from DAM, GDHT and LPV as follows.

A DAM will be carried out by the BIS or the entropy (GE-entropy) monitors and will be initiated before induction of anaesthesia. After induction, maintenance of anaesthesia with halogenated or intravenous agents will be started when EEG-based index will be higher than the value of 55.[30] The EEG-based index values will be then maintained at a target of 50 to ensure adequate hypnotic effect. The suppression ratio (SR) and the burst suppression ratio (BSR), derived respectively from BIS and GE-entropy monitoring, are correlated to EEG burst suppression and associated to deep anaesthesia. RS or BSR values will be maintained at zero during the whole anaesthesia. Indeed, these EEG patterns have been associated with adverse outcomes in intensive care unit (ICU) patients,[31] and the percentage of time with an intraoperative BSR higher than zero is suggested as an independent risk factor for postoperative delirium.[26]

A GDHT will be initiated immediately following induction of anaesthesia by monitoring of stroke volume (SV) measured by an esophageal Doppler probe or by arterial waveform analysis (pulse contour analysis) according to the usual practices of the centre or the reliability of the monitoring device for the patient considered. The strategy is to maximise SV by administering an iterative fluid challenge (200 mL crystalloid in 10 min),[14] until SV no longer increase by 10% in response to each fluid therapy. Then SV will be maintained above 90% of maximal SV throughout the intervention period with crystalloid boluses as required (figure 2).

Mean arterial pressure (MAP) will be maintained above 80% of the patients' baseline mean blood pressure defined as MAP on arrival in the operating room.

An LPV will be initiated associating,[16] a tidal volume of 6–8 mL/kg of the PBW, a PEEP level of 6–8 cmH_2O and a recruitment manoeuvre's applied immediately after

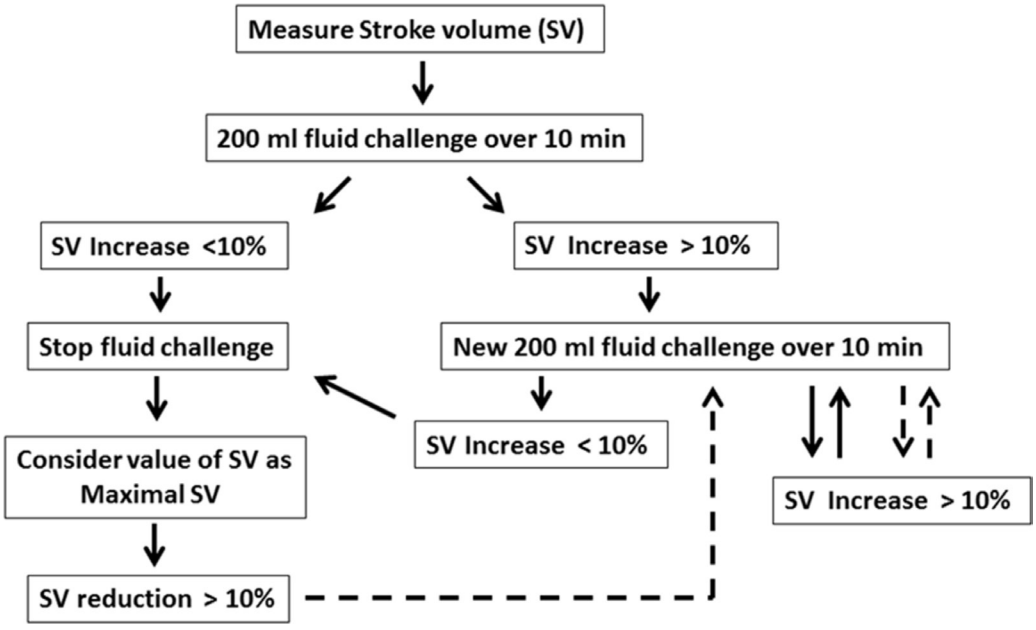

Figure 2 Algorithm for goal-directed haemodynamic therapy. SV, stroke volume.

tracheal intubation and every 30 min thereafter until the end of surgery. PBW will be calculated according to a predefined formula: 50+0.91× (centimetres of height – 152.4) for males and 45.5+0.91× (centimetres of height – 152.4) for females. Each recruitment manoeuvre will consist of applying a continuous positive airway pressure of 30 cm of water for 30 s. During anaesthesia, a plateau pressure of no more than 30 cm of water will also be targeted.

Core temperature will be maintained at 37°C using preoperative checking of the temperature, preoperative and peroperative forced air warming system and warmed intravenous fluids.

A visit or a video conference specifying the exact nature of the optimisation will be performed in each centre only within 15 days preceding the shift from the control period to the intervention period in order to limit modification of usual practice in the management of control patients.

Outcomes

The primary outcome measure will be a composite of mortality or major postoperative morbidity occurring by day 30 after surgery, defined as one or more of the following:

1. Acute kidney injury defined by Kidney Disease: Improving Global Outcomes (KDIGO) stage 1 or higher.[32]
2. Acute myocardial infarction.[33]
3. Heart failure.[34]
4. Stroke.[35]
5. Development of sepsis and septic shock.[36]
6. Acute respiratory failure requiring non-invasive ventilation or intubation.[37 38]
7. Delirium.[39 40]

An identical standardised surveillance will be daily performed in the two groups according to the aforementioned references. In addition, each component of the primary outcome measure will be analysed separately.

Secondary outcome measures will be as follows:

1. Postoperative complications evaluated separately within 7 days and 30 days:
   a. Acute kidney injury.[32]
   b. Cardiovascular complications (myocardial infarction and acute heart failure).[33 34]
   c. Stroke.[35]
   d. Sepsis and septic shock.[36]
   e. Delirium.[39 40]
   f. Pulmonary complications (postoperative hypoxaemia, postoperative pneumonia, acute respiratory failure requiring non-invasive ventilation or intubation and postoperative acute respiratory distress syndrome (ARDS).
   g. Surgical site infection (superficial, deep incisional and organ/space).[41]
   h. Laboratory-confirmed bloodstream infection.
   i. Urinary tract infections.
   j. Pressure sores.[42]
   k. Thromboembolic complications (pulmonary embolism and deep venous thrombosis).
   l. Surgical complications (nature, severity grade[43] and consequences).
2. Length of stay in ICU and the rate of unexpected ICU admission (or readmission).
3. Duration of hospital stay.
4. Early readmission rate at day 30.
5. Readmission rate for the first year.
6. Thirty-day and 1-year postoperative patient autonomy evaluated by the Katz score,[44] and the Lawton Intrumental activities of daily living (IADL) scale[45] (see online supplementary appendices 4 and 5).

7. Rate of home care, hospital-dependent patients and institutionalisation at 1 year.
8. One-year mortality.

Safety

All serious adverse event (SAE) will be reported to the trial coordinating centre. According to the French Public Health Code, all suspected unexpected SAEs will be reported to the the ANSM. In addition, this information will be transmitted to the Data Monitoring Committee (DMC). The DMC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMC is composed of two independent anaesthesiologist experts in large-scale clinical trials and one independent statistician (see online supplementary appendix 6). The DMC members are free of financial interests that could be substantially affected by the outcome of the trial.

The DMC will be responsible for safeguarding the interest of trial participant. It will assess the safety and efficacy of the interventions during the trial and monitor the overall conduct of the trial. The DMC may formulate recommendations relating to recruitment of participants, their management, improving adherence to protocol-specified regimens and the procedures for data management and quality control. The DMC will also provide recommendations about stopping or continuing the trial to the steering committee (SC) of the OPTI-AGED trial. Stopping rules will be as follows:

1. If the occurrence of postoperative complications is higher in the optimisation group than in the control group.
2. If incidence of mortality is higher in the optimisation group than in the control group.

The DMC recommendations will not include a discontinuation of the study for efficacy. The DMC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMC recommendations to determine whether amendments to the protocol or changes in trial conduct are required and to decide whether to continue or terminate the trial.

Statistical analysis

Sample size estimation is based on the 2010 French Hospital Discharge database, programme de médicalisation des systèmes d'information (PMSI) that contains medical procedures for all patients admitted to public and private hospitals identified by their code according to medical classification for clinical procedures and discharge diagnoses encoded in the International Classification of Diseases, 10th revision codes. Patients aged 75 years and older with one or more major comorbidities represented for three different types of surgery (femoral head fracture, major intraperitoneal abdominal surgery lasting >90 min (excluding elective cholecystectomy and abdominal wall surgery), vascular surgery (excluding venous surgery and fistula creation)), a population of 59 865 patients with an in-hospital mortality of 8.5%, a 30-day estimated mortality based on VISION cohort of 12.8%[46] and a 24% rate of the primary outcome. For an individual randomised trial, 1320 patients (n=660 by arm) would be necessary to show a 30% relative difference in the primary outcome, for a two-sided type I error at 5% and a statistical power around 90%, assuming a 24% rate of primary outcome in the control group. The assumption in randomised controlled trials that the outcome for an individual patient is completely unrelated to that for any other patient is violated in cluster randomised trials because patients within any one cluster (centre in our case) are more likely to respond in a similar manner. This similarity is known as the intraclass correlation coefficient (ICC). According to the ICC, values reported usually in the literature ranged between 0.005 and 0.05 ([47,48] and database of ICCs related by the University of Aberdeen http://www.abdn.ac.uk/hsru/research/delivery/behaviour/methodological-research/), steps of randomisation, time periods, average number of patients per centre and lost to follow-up (around 5%), 2500 patients (n=1250 patients by group) will be needed.

Analyses will be performed using Stata software. All data will be analysed by intention to treat. The tests were two sided, with a type I error set at α=0.05. Baseline characteristics (centres and patients) will be presented as the mean and SD or the median and IQR for each randomisation group for continuous data and as the number of patients and associated percentages for categorical parameters. The characteristics of the patients and clusters will be summarised by randomisation group to allow consideration of selection biases and lack of balance. Patients will be described and compared between randomised arms at baseline for eligibility and epidemiological, clinical and treatment characteristics. Compliance with the optimisation procedures will be analysed in the intervention group, and the values of BIS, SR, MAP, SV, VT, fraction of inspired oxygen, PEEP, as well as the recruitment manoeuvres number will be compared in the two groups. Protocol deviations and reasons for withdrawal will be described. Other parameters as the numbers analysed, the average cluster size, cluster characteristics and important patient characteristics will be compared in each cluster by period. To compare the incidence of the primary endpoint (composite of mortality or major postoperative morbidity occurring by day 30 after surgery), a generalised linear mixed model (robust Poisson) will be proposed. Randomisation groups, steps of randomisation, time periods and their interactions were evaluated as fixed effects and centre and time as random effect. Results will be expressed as relative risks and 95% CIs. The estimated intracluster correlation and time effect from the fitted model will be reported. Multivariable analysis will use same statistical model with covariates determined according to univariate results and clinical relevance (type of surgery, American Society of Anesthesiology Score (ASA) score and Charlson comorbidity index, comorbidities and emergent repair). Intergroup comparisons for other endpoints will be performed using same

random effects models taking into account between and within centre variability: linear (if necessary, a logarithmic transformation to access the normality statistical distribution should be envisaged) or generalised linear (acute kidney injury, myocardial infarction, acute heart failure, stroke, systemic inflammatory response syndrome, sepsis and severe sepsis, septic shock, delirium, postoperative pulmonary complications, rate of unplanned ICU hospitalisations, rate of early rehospitalisation at follow-up day 30 and rate of rehospitalisation within the first year). Postoperative pulmonary complications (pneumonia, postoperative hypoxaemia, pulmonary embolism, atelectasis, development of acute lung injury (ALI/ARDS), pneumothorax and need for postoperative ventilation (invasive and/or non-invasive ventilation) for postoperative respiratory failure at any time after surgery) will be analysed separately (as components of composite primary criteria), using the Hochberg procedure to consider type I error inflate. The time-to-event curves will be calculated with the Kaplan-Meier method and compared, when appropriate, using marginal Cox proportional hazards regression model (1-year mortality). Length of stay in ICU or in hospital will be considered in a competing risk. The random effects models were also used to study longitudinal repeated data (30-day and 1-year postoperative patient autonomy evaluated by the Katz score, Lawton IADL scale and rate of home care and hospital dependent patients) considering subject patient as random effect in addition to centre. According to clinical relevance and to European Medicines and CONSORT recommendations, subgroup analyses depending on hip fracture will be proposed after the study of subgroup×randomisation group interaction in regression models. Finally, the statistical nature of missing data will be studied, and sensitivity analysis will be proposed to analyse the impact of missing data on results and propose the most appropriate method of imputation

Data registration

Data entry will be performed under the responsibility of the investigator at each participating centre, by him or clinical personnel into a secured web-based electronic case report form (eCRF) (Ennov Clinical, Ennov, Paris, France). Automated validation checks included plausibility ranges and cross-checks between data fields. Data collection will be monitored by trained research coordinators. Missing data or specific errors in the data will be summarised along with detailed descriptions for each specific problem in Data Query Reports addressed to investigators.

Data will be recorded as the day of inclusion, the day of surgical procedure and then at 7 days, at the end of hospitalisation, at 30 days and 1-year postoperatively. If the patient is still present in hospital on day 7, follow-up will be continued until hospital discharge. If the patient leaves hospital before day 7, the 7th day data collection will not be carried out. The trial flow chart is presented in figure 3.

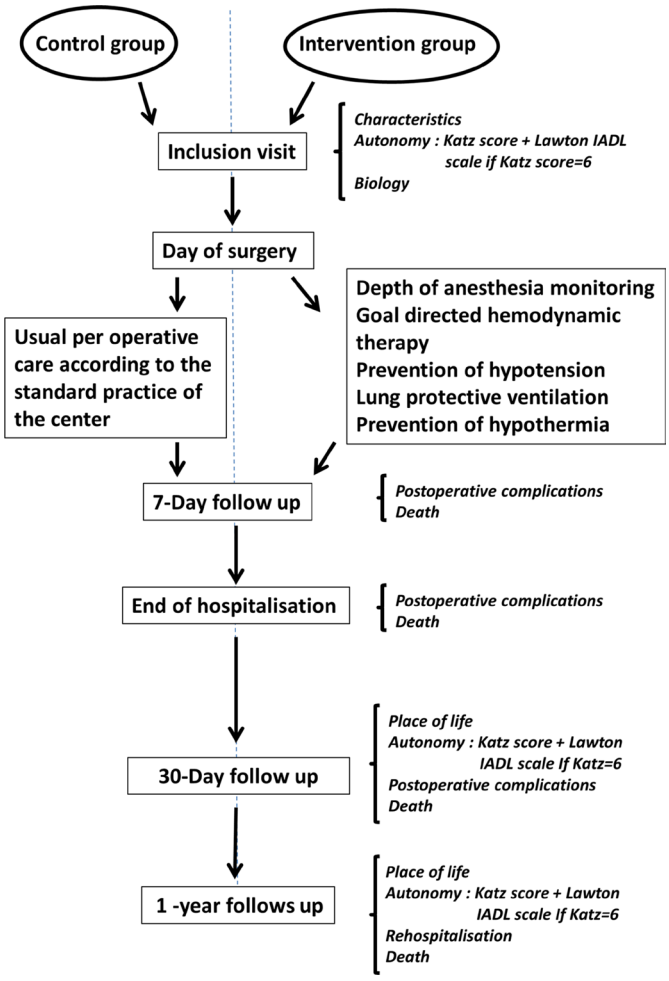

Figure 3 Trial flow chart.

The following data will be registered at inclusion visit:

Date of inclusion, date of birth, examination of the eligibility, exclusion and selection criteria. Baseline characteristics: demographic data (age, height, weight, gender, and body mass index); comorbidities (ischaemic coronary disease: Y/N; cardiac arrhythmia: Y/N; congestive heart failure: Y/N; peripheral vascular disease: Y/N; dementia: Y/N; stroke: Y/N; chronic obstructive pulmonary disease: Y/N; chronic respiratory failure: Y/N; chronic alcohol abuse: Y/N; active cancer: Y/N; and diabetes: Y/N; chronic renal failure: Y/N), Charlson comorbidities score; ASA score; and type of surgery.

Patient's functional status of independency assessed by Katz score and Lawton IADL scale in case of Katz score=6.

Biology: blood sodium, chloride, urea, creatinine and haemoglobin.

During the surgical procedure, the following data will be collected:

Type of surgery, type of haemodynamic monitor if applicable (oesophageal Doppler: Y/N; pulse contour: Y/N; other: Y/N). Anaesthetic data collection during the surgical procedure is presented in table 2.

Daily from postoperative day 1 (08:00) to day 7 after surgery and at hospital discharge, the following data will be collected:

Table 2 Overview of the two periods peroperative anaesthetic data collection

Parameters	Control period	Intervention period
Preanaesthesia induction		
HR	√	√
SAP, MAP and DAP	√	√
SpO_2	√	√
Bispectral index (BIS) or state entropy (SE) index value	*	√
Anaesthesia induction		
Type of anaesthetic agents	√	√
Time	√	√
Following anaesthesia induction		
HR	√	√
SAP, MAP and DAP	√	√
SpO_2	√	√
BIS or SE index, SRor BSR	*	√
SV maximisation time	*	√
MSV	*	√
T°	*	√
First recruitmentmanoeuvre time	*	√
Surgical incision time	√	√
Anaesthesia maintenance		
Type of anaesthetic agents	√	√
Time of halogenated agent introduction (BIS/SE, SR/BSR corresponding values)	√(*)	√(√)
VT, PEEP, FiO_2	√	√
BIS or SE index/10 min	*	√
SR or BSR/10 min	*	√
MAP/10 min	*	√
SV/10 min	*	√
Recruitment manoeuvres/30 min	*	√
Blood loss and Hb determination/hour	*	√
End of anaesthesia		
Timing (end of surgery, end of anaesthesia and extubation)	√	√
Number of recruitment manoeuvres	*	√
T°	√	√
Use of adrenergic agents (Y/N)	√	√
Filling volume and type (crystalloids, colloids and blood cells)	√	√
Postinterventional destination	√	√

*Optional according usual peroperative care.
BSR, burst suppression ratio; DAP, diastolic arterial pressure; FiO_2, fraction of inspired oxygen; Hb, haemoglobin; HR, heart rate; MAP, mean arterial pressure; MSV, maximal stroke volume; PEEP, positive end-expiratory pressure; SAP systolic arterial pressure; SpO_2, pulse oxygen saturation; SR, suppression ratio; SV, stroke volume; T°, temperature; VT, tidal volume.

1. Postoperative care pathway (surgical ward: Y/N, high dependency intensive care unit (HDU): Y/N, ICU: Y/N).
2. Postoperative complications (Y/N, type and date of diagnosis, consequences).
3. Transfusion of pack red blood cells: Y/N.
4. Unplanned HDU or ICU admission at any time: Y/N.
5. Length of stay in HDU, ICU and surgical ward.
6. Unexpected SAE and death (Y/N and date).
7. Date of hospital discharge and hospital discharge destination (home or preoperative living place, geriatric unit, mid or long stay hospitalisation and care home for dependent elderly).

Thirty days after surgery:

All patients will be contacted at day 30 either by telephone for those who had left the hospital or by visit for those who had not. When necessary, investigators will contact community physicians or other hospitals for outstanding information describing the primary outcome.

1. Date.
2. Place of life.
3. Postoperative complications (Y/N, type, date of diagnosis and consequences).
4. Patient's functional status of independency assessed by Katz score and Lawton IADL scale if Katz score=6.
5. Unexpected SAE and death (Y/N and date).

One year after surgery:

1. Date.
2. Place of life.
3. Patient autonomy evaluated by Katz score and Lawton IADL scale if Katz score=6.
4. Unexpected SAE and death (Y/N and date).

End of study:

1. Date.
2. Completion of the study (Y/N). If no: lost to follow-up and refusal of continuation of the study.
3. Date of last patient news.

Adherence to intervention protocol

Adherence to intervention protocol will be checked weekly in each centre by a member of the Trial Management Committee (MB) (see online supplementary appendix 6). Adherence reminder sessions will be organised consequently if necessary.

Quality of data

In accordance with the CHU Saint-Etienne Standardized Operating Procedures as well as the GCP guidelines and the in force legislation and laws, a clinical research assistant will be in charge of the study. He will ensure compliance with the clinical trial protocol and its described procedures, make on-site visits (opening and closing visits) and planned quality control monitoring visits to review the collected data into the eCRF (accuracy, missing data, consistency between these data and those of 'source' (medical files, original of the laboratory results and so on)).

In each centre, a technician of clinical research will be in charge of patient screening, filling eCRF and management of study medical devices.

Recruitment

The strategy for achieving adequate participant enrolment to reach target sample size was based on centre selection. Analysis of the French Hospitals Discharge Database (PMSI) allowed selecting centres with an annual recruitment of at least 1000 patients aged 75 years and over for the selected surgeries. A preliminary study performed in each pre-empted centre over 30 days allowed to determine its potential of recruitment. The number of patients to be included for a given centre was only 10% of the patients included in the preliminary study.

Data handling, confidentiality and retention

Data will be handled according to the French law. Data recording will be done into a secured electronic system via a web navigator on a hosted eCRF (and saved on a daily basis) by a service provider and protected by an individual password for each investigator that will be changed every 3 months. Participant's identifying information will be replaced by an unrelated sequence of characters to ensure confidentiality. The SC will have access to the full trial dataset. Site's lead investigators will have access to the full dataset if a formal request describing their plans is approved by the SC. All original records (including consent forms, reports of suspected unexpected SAEs) will be stored for 15 years at the trial sites. The clean trial database file will be maintained for 15 years.

Patient and public involvement

Patients were not involved in the design or the conduct of the study. The burden of the intervention was not assessed by the patients themselves.

Participant's retention

It is projected that the rate of loss to follow-up will be around 5% at the end of the study following the 1-year evaluation. To achieve this level of follow-up in each centre, a 6-month contact with the patient, his family or his legal representative will be performed by the technician of clinical research reminding them of the upcoming data collection.

Enrolment and timeline

The trial will be conducted in 27 French university and non-university hospitals during a 2-year period starting in March 2017. One year of patient follow-up will be added at the end of inclusions. Cleaning and closure of the database will be carried out at 2020. Data analysis, manuscript writing and submission for publication will follow at the end of 2020. Recruitment began on March 2017. On 19 February 2018, 981 patients were included.

Protocol amendments

The SC will be responsible for the decision to amend the protocol. Any modifications to the protocol or significant administrative aspects will require a formal amendment to the protocol. Each amendment will be approved prior to implementation by the regional ethic committee and notified to the health authorities in accordance with French regulation.

Dissemination policy

The data from all OPTI-AGED sites will be analysed study-wide and reported as such. An individual centre is not expected to report the data collected from its centre alone. The SC will give the timing of presentation of endpoint data and the meetings at which they might be presented and will also determine the publication policy. Authorship for manuscripts submitted for publication will follow the criteria defined by the International Committee of Medical Journal Editors (available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

DISCUSSION

There is an increasing awareness that intraoperative care may contribute to postoperative adverse outcomes, but there are few large clinical trials evaluating the risks and benefits of specific anaesthetic interventions and none, to our knowledge, measuring the advantages of a multi-modal optimisation strategy. A strategy combining haemodynamic intervention, LPV and EEG monitoring of anaesthesia depth may be valuable to improve outcome in high-risk groups of patients and especially in the elderly. The objectives of haemodynamic optimisation are to maintain tissue perfusion, and to ensure intra-operative optimisation of oxygen delivery. Titration of depth of anaesthesia, by decreasing anaesthetic dosage, contributes to minimise cardiovascular depression, deep anaesthesia periods and to maintain adequate organ perfusion and function. LPV allows improving postoperative oxygenation by limiting the occurrence of intraoperative atelectasis and reducing pulmonary inflammatory response. The integration of each of these elements into the perioperative management of elderly patients can be beneficial to eliminate any build-up of oxygen debt during anaesthesia for this increasingly vulnerable surgical population. Performing the OPTI-AGED trial is in line with the 2011 recommendations of the Anaesthetists of Great Britain and Ireland on the use of combined depth of anaesthesia and flow monitoring for managing proximal femoral fractures in elderly. This trial will also specify whether or not any reduction in postoperative morbidity is associated with a long-term change in the elderly patient's autonomy. The results of this study may support future healthcare of elderly surgical patient and its socio-economic impact.

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Contributors All authors made substantial contributions to the OPTI-AGED trial and gave final approval of the manuscript. SM drafted the manuscript with SP and BP. SM designed the study together with EF and YL. Trial design refinement and sample size calculation were determined by YL and BP. BP planned the statistical analysis. SM is the principal investigator and coordinator of OPTI-AGED. SM, SP, EF, YL and BP are members of the steering and trial management committee. MB and FR are members of the trial management committee.

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Patient consent Obtained.

Ethics approval The study was approved for all coinvestigator centres by the institutional review board of Saint-Etienne University Hospital, as well as the regional ethics committee ('Comité de Protection des Personnes Sud-Est 1') on 13 June 2016 with registration number 2016–24.

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