

# Perioperative interventions and postoperative outcomes

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Für Anna.

## **Scientific environment**

The work is a part of the Research group on Quality, Safety and Outcome after Surgery and Critical illness (ROSC) at the Department of Clinical Medicine, University of Bergen, in close cooperation with the Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen Norway. The group was established in 1999 and is one of the most active in Europe within this field. The work of the group is closely related to the subjects of patient safety and quality of care.

This PhD opened the research profile to include outcomes after major surgery since both scheduled stay and postoperative complications represent important parts of intensive care patients. I have in addition worked closely with a research group at The Queens University of London, led by Professor Rupert Pearse who has a main role in postoperative outcomes research within Europe.

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# Abstract

**Background:** Postoperative complications are frequent causes of postoperative mortality. Such complications may also lead to a prolonged period with decreased functional and cognitive status. Perioperative care is a factor in postoperative morbidity and mortality. Until now no common international definitions and classifications of postoperative complications have been established.

The group of surgical patients with the highest risk of postoperative complications accounts for perhaps 80% of intra-hospital deaths. With the high volume of surgery performed worldwide, even a slight reduction in complications would result in a lower number of preventable deaths. There are several theories on how to decrease postoperative complications and improve patient safety and patient care. Two factors, checklists and perioperative fluid balance, are investigated in this thesis.

## **The overall aim of this thesis is twofold:**

1. To study perioperative complications and outcome after major surgery
  - Paper I aimed at creating standard definitions of outcome measures for use in pragmatic large perioperative clinical trials.
  - Paper II aimed at providing data on perioperative mortality after non-cardiac surgery across Europe.
2. To contribute in finding ways to reduce complications after major surgery
  - Paper III aimed at identifying the prevalence of surgical checklist use and possible relationship with mortality.
  - Paper IV aimed at evaluating the effect of perioperative goal directed fluid therapy guided by ScvO<sub>2</sub> in open colorectal surgery.

**Result: Paper I** was a literature review to assess the current state of knowledge about surgical outcome definitions. A standardized list was created for use in perioperative research and clinical audit. The outcome measures described are organized into four different categories: Individual adverse events, Composite outcomes, Grading of complications and Health related quality of life.

**Paper II** was a 7 day cohort study (European Surgical Outcome Study) conducted in 498 hospitals across 28 European countries. Intra-hospital mortality data was registered for all adult patients undergoing non-cardiac surgery. The overall intra-hospital mortality throughout Europe was 4%. A variation in mortality after surgery throughout Europe could be confirmed. This may indicate a discrepancy in standard of care. Identification and standardisation of key factors in perioperative care would subsequently improve outcome throughout Europe.

**Paper III** determined the point prevalence of checklist use in Europe and its association with in-hospital mortality, using data collected from the European Surgical Outcome Study. There was a marked variation between checklist use and mortality in Europe. The use of a surgical checklist was associated with lower mortality. Although there is no causality demonstrated, checklist use may be an indicator of hospitals focusing on improved perioperative care and therefore decrease mortality.

**Paper IV** investigated the use of goal directed fluid therapy in 241 patients undergoing abdominal surgery and its influence on postoperative morbidity. Patients were randomized in a control group receiving standard fluid therapy and an intervention group using central venous oxygen saturation as a surrogate for cardiac output to guide fluid therapy. Although there was a difference in the amount of fluid given between the two groups, the complication rate 30 days after surgery was equal.

**Conclusion:** We proposed standardised outcome measures for use in future trials investigating postoperative complications. This contributes to a meaningful comparison of quality of care in future clinical trials and leaves less room for interpretation of outcome measures. It is not likely that one single intervention in the perioperative period will markedly affect outcome. Most likely a multifactorial intervention will be successful in reaching this goal. However, specific research in the high-risk surgical population is lacking. It can be assumed that this patient group would have the greatest benefit from an improved perioperative care pathway.

Better data may be available after foundation of national and international perioperative registers. This may help to establish a greater research community in

perioperative outcome research and assist to identify factors in the perioperative care pathway that improve outcome.



# List of publications

## *Paper I:*

Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, Leva B, Rhodes A, Hoefft A, Walder B, Chew MS, Pearse RM.

***Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measures.***

Eur J Anaesthesiol. 2015 Feb;32(2):88-105. doi: 10.1097/EJA.000000000000118.

## *Paper II:*

Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent JL, Hoefft A, Rhodes A; European Surgical Outcomes Study (EuSOS) group for the Trials groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology.

***Mortality after surgery in Europe: a 7 day cohort study.***

Lancet. 2012 Sep 22;380(9847):1059-65. doi: 10.1016/S0140-6736(12)61148-9.

## *Paper III:*

Jammer I, Ahmad T, Aldecoa C, Koulenti D, Goranović T, Grigoras I, Mazul-Sunko B, Matos R, Moreno R, Sigurdsson GH, Toft P, Walder B, Rhodes A, Pearse RM; for the European Surgical Outcomes Study (EuSOS) group.

***Point prevalence of surgical checklist use in Europe: relationship with hospital mortality.***

Br J Anaesth. 2015 May;114(5):801-7. doi: 10.1093/bja/aeu460.

## *Paper IV:*

Jammer I, Ulvik A, Erichsen C, Lødemel O, Ostgaard G.

***Does central venous oxygen saturation-directed fluid therapy affect postoperative morbidity after colorectal surgery? A randomized assessor-blinded controlled trial.***

Anesthesiology. 2010 Nov;113(5):1072-80. doi: 10.1097/ALN.0b013e3181f79337.

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# 1. Introduction

## 1.1 Outcomes after surgery

More than 230 million surgical procedures are performed worldwide each year [1, 2]. Health care systems around the world work hard to improve outcome for patients after surgery. Health authorities may offer monetary incentives for hospitals to introduce treatments that may have been proven to improve outcome of patients. These treatments focus on improving efficiency, reducing length of stay (LOS) and offering better service to patients. Standardized treatment protocols are increasingly introduced to ensure adherence to treatment plans and to reduce variability in care [3].

There are indications that perioperative care is a factor in postoperative mortality [4]. Postoperative complications are frequent causes of postoperative mortality. Such complications may also lead to a prolonged period with decreased functional and cognitive status. Postoperative complications can have a huge impact on hospital costs [5]. It is therefore quite surprising that until now no common international definitions and classifications of postoperative complications have been established.

The risk of complications and death during the postoperative period is low in healthy patients [6]. But patients with the highest risk of developing postoperative complications representing 80% of intra-hospital deaths according to studies performed in the UK [2, 7]. With the high volume of surgery performed worldwide, even a slight reduction in complications would result in a lower number of preventable deaths.

There are several theories on how to decrease postoperative complications by improving patient safety and patient care. Some of the interventions studied include: perioperative temperature control, perioperative oxygen delivery, perioperative fluid balance, use of checklists, early mobilisation, prehabilitation and Early Recovery After Surgery (ERAS).

Two of these factors, checklists and perioperative fluid balance, are investigated in this thesis.

Outcomes after surgery can be divided in mortality and non-mortality outcomes.

## 1.2 Mortality after surgery

Mortality is a binary outcome: The patient is either dead, or alive. This is in itself easy to measure. There is, however, considerable variation in length of follow up periods in previous studies. Unless similar follow-up time is used, it is not possible to make a legitimate comparison of mortality rates. The most common follow up periods are either 30 days or in-hospital mortality [8]. Many UK health registries monitoring surgical morbidity do not perform follow up after hospital discharge [8].

Mortality is often considered the most important outcome measure. But measuring a change in gross mortality in patient populations with low mortality is not necessarily the primary outcome. Additionally the large population size required to measure small changes in mortality may not be available. Furthermore, perioperative interventions often aim to prevent specific complications or categories of events which are more relevant to study than mortality.

### 1.2.1 Mortality and type of surgery

Khuri et al. did a retrospective study analysing the National Surgical Quality Improvement Program (NSQIP) database on the occurrence of postoperative complications and 30-day mortality. A total of 105 951 patients undergoing one of eight defined operations between 1991 and 1999 were studied. Included operations were abdominal aortic aneurism, infrainguinal vascular reconstruction, carotid endarterectomy, colectomy, open cholecystectomy, laparoscopic cholecystectomy, pneumectomy and total hip replacement. They found an overall 30-day mortality in the study population of 3.07% with a variation from 0.55% for laparoscopic cholecystectomy to 6.51% for colectomy [9].

## **1.2.2 Mortality and perioperative complications**

Complications in the perioperative period are known to be important causes of mortality [9-11].

Kamphues et al. compared 428 patients who underwent resection of pancreatic cancer and found that the occurrence of a severe postoperative complication shortened median survival significantly (16,5 vs. 12,4 months;  $p=0.002$ ) [10].

Khuri et al. found that postoperative complications are an independent factor for postoperative 30-day mortality [9]. The effect of postoperative complications on mortality lasts over time: The occurrence of a complication within the first 30 days after surgery reduced median patient survival by 69% during a five year follow up in the total study group. This effect was independent of preoperative risk factors, making a postoperative complication a better predictor for long time mortality than preoperative risk [9].

A UK study on the association between perioperative complications and mortality after major surgery analysed data from 1362 patients. Median follow up time was 6.5 years. The mortality of all included patients was 1.1% after 30 days, 6.8% after one year and 20.7% after five years. The authors found a relative hazard of death after a postoperative complication of 3.51 during the first year after surgery and 2.44 for the next two years. They state that prolonged postoperative complications are a valid quality indicator for surgical healthcare [12].

## **1.2.3 Mortality and standard of care**

Ghaferi et al. used data of the NSQIP program and compared the association between postoperative complications and in-hospital mortality in 84 730 high-risk patients undergoing general and vascular surgery between 2005 and 2007. In-hospital mortality across hospitals varied from 12,5% to 21.4%. However, hospitals with either very-high or very-low mortality had similar overall complication rates, 24.6% and 26.9%, respectively. This indicates most likely a difference in patient care between hospitals

and suggests that implementation of measures to standardize patient care may reduce mortality [13].

Symons et al. found a significant variation between UK hospital trusts in mortality of high-risk emergency surgical patients. Of 367 796 patients included, the overall 30-day mortality rate was 15.6% with an institutional range of 9.2% - 18.2%. Intensive care bed resources and greater use of computer tomography were independent predictors of reduced mortality [14]. This variation in mortality of emergency surgical patients may also indicate a variation in standard of perioperative care. Standardisation of care and equal access to health care may reduce this variability by improving outcome.

Postoperative critical care after cardiac surgery normally follows a standardized and efficient care pathway guided by strong evidence based practice. Elective cardiac surgery has good outcome data and the overall mortality is low [15].

Performing audit on perioperative outcome data helps to identify and prioritize practice that possibly improves perioperative care. However, good international comparative outcome data is lacking in the general non-cardiac surgical population.



## 1.3 Non mortality outcomes after surgery

Patient centred outcomes focus on the patient wellbeing and possible health deteriorations after an intervention. These can be outcomes like Quality of Life (QoL), functional status, cognitive impairment, reduced organ function, delirium, anxiety and depression. These measures place the value of surgery into the patient's context and reflect outcomes that matter most for patients. The ideal outcome for a patient may be the composite of survival, good function and quality of life. For patients QoL and functional status after a longer period of time are more relevant outcomes than mortality. These patient centred outcomes may be better endpoints in research trials where mortality is low.

### 1.3.1 Hospital length of stay

There are several outcomes used as quality measures after surgery. The most commonly used is hospital length of stay (LOS). A prolonged hospital stay after surgery is assumed to be an indicator of an adverse event in the perioperative period. However, the quality of this indicator is questionable since hospital stay is related to other factors than just perioperative care. It is dependent on the availability of community health service, the bed availability in the hospital, discharge routines and cultural factors.

### 1.3.2 Biomarkers

Various biomarkers in the perioperative period are being used as outcome measures, for example measuring postoperative renal function, myocardial injury or inflammation [16-18]. In this context such markers are mostly used for risk prediction rather than defining outcome after surgery.

### 1.3.3 Classification and definitions of outcome measures

The major challenge in non-mortality outcomes research is the lack of common classifications and definitions.

A Cochrane systematic review included 31 studies on hemodynamic management and its influence on postoperative outcome [19]. The authors stated: *“No two studies used the same list of morbidities after surgery. In most cases, no specific criteria were listed for morbidities. No two studies used the same criteria.”*

All studies in question defined their own list of possible postoperative outcome measures. And even when the same event was described (e.g. congestive heart failure or infection) the definition of the event was different in every study or was not clear.

This obvious heterogeneity in outcome definitions is unfortunate. Studies addressing the same clinical question cannot be compared directly. It also prevents the possibility of pooling data from different papers in meta-analysis, and undermines findings and conclusions.

The need for standardisation of outcome measures was described already in 2001 when Bruce et al. identified four important adverse events that most frequently occurred after abdominal surgery [8]. The adverse events chosen were surgical wound infection, anastomotic leak, deep vein thrombosis (DVT) and surgical mortality. The aim was to find a definition for these four outcome measures.

For surgical wound infection they describe 41 different definitions and 13 grading scales extracted from 82 studies. The authors point out the lack of systematic monitoring of surgical wound infections after hospital discharge.

A similar variation of definitions was found in anastomotic leakage. Here they describe 40 different definitions extracted from 107 papers.

Regarding deep vein thrombosis the authors were not able to do a review due to the vast amount and variation of the available literature. A critical appraisal of the available literature would have gone beyond the scope of their review, so they recommended a separate review to address the definition of deep vein thrombosis [8].

“What is a postoperative complication?” The question is not easily answered. In 2008 Sokol et al. made an attempt to find a definition. They came to the conclusion that “A

*surgical complication is any undesirable, unintended, and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as could reasonably be hoped” [20].* It soon became apparent that this was not an exhaustive definition. It remains unclear for example who decides what is undesirable or unintended. This publication from Sokol et al. resulted in several comments discussing the shortage of his definition and illustrating the difficulty of finding a common description [21-27].

## 1.4 Postoperative complications

### 1.4.1 Type of postoperative complications

Postoperative complications are commonly classified by either a severity score (e.g. mild affection of the patient and not demanding treatment, demanding treatment, and causing disabilities) or by the type (e.g. pneumonia, ileus, wound infection).

Composite outcomes collect types of complications into one entity, e.g. myocardial infarction; congestive heart failure and arrhythmia can be compiled into the single outcome “cardiac event”. The benefit is an increased event rate helping to reach an adequate statistical power without increasing the sample size of study populations.

### 1.4.2 Severity of postoperative complications

Clavien et al. proposed a classification of complications with a grading system and validated the system on a patient cohort [28]. The resulting Clavien-Dindo grading score classifies postoperative complications according to severity [28, 29].

This system consists of five severity grades: Grade I includes minor risk that resolves spontaneously or requires treatment with antiemetics, analgetics, diuretics, fluids or physiotherapy. Grade II complications need intervention in form of other pharmaceutical treatment than named in Grade I. Grade III are potentially life threatening complications requiring surgical or radiological interventions. Grade IV complications need additional ICU management while Grade V is the death of a patient. The Clavien-Dindo grading system is validated and, due to its simplicity and logic, accepted in the field of surgery [30].

In their paper, Clavien et al. additionally postulate that the term “Major” or “Minor” in outcome reporting should be discontinued. These terms are misleading since there is no standardisation of its use. *“There are almost as many definitions for those terms as the number of investigators”* [30]. The unclear definition of the terms “major”, “moderate” and “minor” may also open up for manipulation of data.

The Clavien-Dindo score classifies complications by severity, but does not present a set of possible postoperative complications.

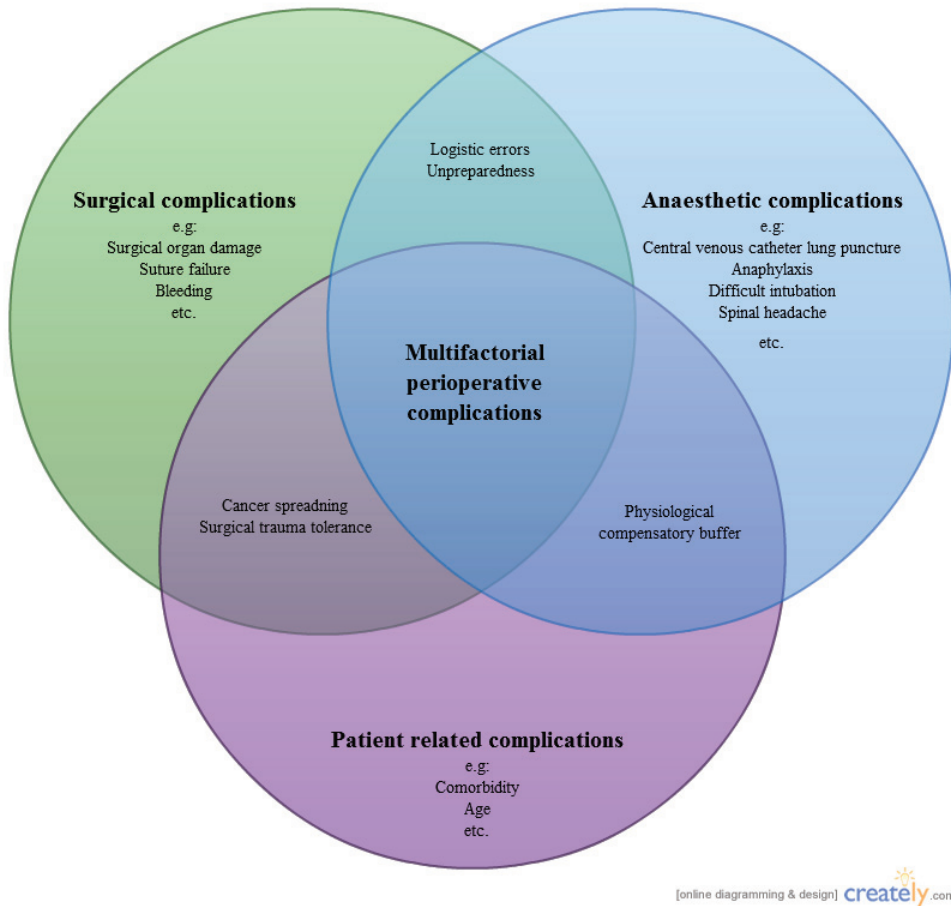
The absence of clear definitions of postoperative complications makes research on the prevalence on specific complications difficult [30]. When reporting outcome data, there should be little room for subjective interpretation or mistakes [31].

There is thus a clear need for a robust and standardized set of outcome definitions to use in the perioperative period, and also guidance on the time period over which they should be applied.

### **1.4.3 Identification of postoperative complications**

The identification of the origin of postoperative complications is a key to their prevention. Ideally it should be possible to classify a complication according to its origin. However, most complications arising after surgery are multifactorial and cannot be backtracked to a single event. Some of these complications are caused by intraoperative factors. For example postoperative pneumonia can arise due to micro aspiration during intubation, long surgery, prolonged ventilator therapy, atelectasis, postoperative inactivity and lack of coughing drive due to pain or sedation. The occurrence of a postoperative complication is therefore in most cases a multifactorial event. For simplicity we keep the term “postoperative complications” as a common concept, even though some complications become evident intraoperatively.

An example of the influence of different perioperative factors on multifactorial complications can be seen in Figure 1.



*Figure 1: Venn diagram illustrating different entities that may affect postoperative outcome. Although some complications may have its origin in only one of the areas, (e.g. microaspiration due to difficult intubation resulting in postoperative pneumonia), are most complications a result of a multifactorial event in the perioperative period (e.g. patient has a lung disease and is therefore more susceptible for pneumonia after microaspiration)*

#### **1.4.4 Surgical complications**

Surgical complications arise due to undesirable events connected to the surgical procedure itself. Research in surgical outcomes concentrate mostly on the organ operated on and follow up of patients is focused on function of the site operated on, e.g. hip fracture or liver surgery.

An outcome that is inherent with the surgical procedure should not be confused with a complication. Clavien et al. have considered this as a sequelae [29]. As an example: A scar after surgery may be undesirable but is a consequence of the surgical procedure and not necessarily a complication.

#### **1.4.5 Anaesthetic complications**

Anaesthetic complications are connected to the anaesthesia procedure itself. This could for example be failure to intubate, anaphylaxis or iatrogenic pneumothorax after insertion of a central venous catheter.

#### **1.4.6 Patient related complications**

Patient related complications arise due to pre-existing comorbidities that may affect outcome after surgical stress. It could be drug abuse, age, ongoing cancer disease etc. These comorbidities are often used as indicators for developing a complication in risk prediction scores.

#### **1.4.7 Multifactorial complications**

Although some complications are related to only one of the fields above, the majority of complications have a multifactorial background. They can be related to perioperative errors or small hits occurring during the perioperative pathway that in the end result in a complication. Analysing the origin of all sorts of perioperative complications is beyond the scope of this thesis.

## 1.5 Prevention and reduction of perioperative complications

There are numerous interventions that aim to prevent organ specific complications. Following is an overview of the most common single interventions aiming to prevent postoperative complications. At the end of this chapter two interventions are summarized (fluid therapy, checklist use) that are investigated in this thesis.

### 1.5.1 Meeting oxygen demand

Disturbances in myocardial perfusion and imbalances in oxygen demand and delivery may lead to cardiac complications after noncardiac surgery. A short episode of a mean arterial pressure less than 55 mmHg preoperatively increases the the risk of myocardial injury and acute kidney injury [32]. Perioperative myocardial injury and acute kidney injury can have a substantial impact on postoperative mortality [17, 33]. Maintaining a mean arterial pressure above 55 mmHg may therefore decrease postoperative complications.

A metaanalysis demonstrated that a high intraoperative oxygen fraction ( $\text{FiO}_2$ ) may reduce the incidence of surgical site infections [34]. The increased oxygen tension in the tissue may lead to an increased oxidative killing of surgical pathogens, resulting in a drop of surgical site infections. However, the effect size is small and the studies included are heterogeneous including confounding factors the authors were unable to correct for. Perioperative hyperoxemia may even be harmful by increasing long time mortality in cancer patients [35]. Consequently hyperoxemia during surgery is not advised.

Giving the right amount of fluid in a goal directed manner may maintain cardiac output and therefore maintains oxygen delivery, see chapter 1.5.9.

### 1.5.2 Maintaining normothermia

Induction of anaesthesia or poor thermal insulation of the patient may lead to peroperative hypothermia. This is associated with perioperative complications like surgical wound infections [36] or coagulopathy [37]. Hypothermia alters drug



metabolism, leading to increased duration of muscle relaxants and a change in pharmacokinetics of Propofol [38]. Active warming of patients undergoing prolonged surgery is therefore mandatory.

### **1.5.3 Protecting the lungs**

High PEEP and high tidal volume with recruitment manoeuvres have been investigated, suggesting having a protective effect against atelectasis. However, they have shown no benefit in decreasing postoperative lung complications [39, 40]. Therefore a lung protective strategy with low PEEP and low tidal volume is recommended during anaesthesia.

After major surgery, patients at risk can be treated with noninvasive continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) Oxygen therapy. Both therapies may prevent postoperative respiratory failure and decrease reintubation rate [41-43].

Physiotherapy before surgery and early mobilisation after surgery can prevent postoperative complications of the lung. However, most studies are low quality or non-randomized trials and resulting recommendations are mostly expert opinions [44].

### **1.5.4 Prehabilitation**

An emerging concept within perioperative care is surgical prehabilitation. It derives from the realisation that the preoperative time from decision to surgery until the day of surgery can be used to enhance the functional, physical, nutritional and psychological status of the patient. This strengthens the patient to tolerate the upcoming physiological and surgical stress [45, 46]. However, this area of research is relatively young and published studies have a significant risk of bias. The effect of prehabilitation must therefore be scrutinized with caution [47].

### **1.5.5 Avoiding postoperative delirium**

Delirium is common in the perioperative period. A number of risk factors have been identified in the development of delirium, including, history of psychiatric illness,

lower preoperative functional status, advanced age and pre-existing cognitive impairment. The impact of delirium on unfavourable postoperative outcomes is significant and extends beyond the immediate postoperative period [48, 49]. In an older medical population, delirium is an independent predictor of increased 12 month mortality [50].

Several drugs have been investigated in preventing delirium, but the results are not robust enough to suggest general pharmacological prevention to other than individual high-risk patients [51].

The nonpharmacological prevention and treatment of delirium is complex. It requires an individualized intervention delivered by a multidisciplinary team addressing cognitive impairment, disorientation, dehydration, constipation, poor nutrition, sensory impairment and promote good sleep [52]. As a result, a multimodal, nonpharmacological approach prevents delirium, avoids institutionalisation and is cost effective [53].

### **1.5.6 Postoperative pain treatment**

Studies investigating the effect of postoperative pain relief on outcome fail to demonstrate a significant impact on length of hospital stay or mortality despite beneficial effects on physiological responses [54]. However, optimized dynamic pain relief is standard in perioperative care and studies therefore difficult to conduct.

### **1.5.7 Preventing embolism**

The benefit of low molecular weight heparins in preventing perioperative venous embolism is indisputable. However, the benefit of graduated compression stockings has been challenged in medical patients. The significance of this finding is unsettled in surgical patients [55]. New oral anticoagulants may be effective preventing both arterial and venous embolism but there remain safety issues in their use: There exist no antidote, no monitoring, no standardisation in use during the perioperative period and they may increase perioperative bleeding [55].

### **1.5.8 Use of a perioperative checklist**

Improving communication in the operation theatre may enhance detection of errors and therefore prevent adverse events [56, 57]. Using checklists has its origin from aviation, where the introduction helped pilots to manage the complex processes of starting, flying and landing a plane in a safe way. It was postulated that the introduction of a checklist into a similar complex system, such as the operation theatre, would also improve safety by standardizing processes and facilitate communication [58].

The World Health Organisation (WHO) initiated the Second Global Patient Safety Challenge: “Safe Surgery Saves Lives” in 2008. This resulted in the design of the “WHO Surgical Safety Checklist” [59]. It was piloted in 8 hospitals worldwide during 2007-2008 as a cohort study to evaluate its effect on morbidity and mortality. Implementation of the WHO surgical safety checklist was associated with a decrease of the adverse event rate from 11% to 7%. Mortality was reduced from 1.5% to 0.8% [60]. Other studies confirmed these findings with a reduction in mortality [61-63] and complications [61, 62].

Despite the low cost and the possible positive effects on patient outcome, the surgical checklist has not been introduced throughout many different health care systems. There may also be a wide variation in use of checklist within different countries. This opens for the opportunity to study the prevalence of a surgical checklist over different health care systems and its effect on outcome.

### **1.5.9 Optimizing fluid therapy**

Optimizing fluid load during surgery is another area of research proposed to improve perioperative outcome. Giving the right amount of fluid at the right time to compensate for fluid loss seems physiological plausible [64].

Hypovolemia can lead to hypoperfusion of organs and increases mortality in surgical patients [65]. As little as 10% circulating volume deficit may lead to hypoperfusion and reduced peripheral oxygen delivery [66].

It has become standard treatment to administer intravenous fluid perioperatively to compensate for assumed fluid loss and to improve oxygenation by increasing cardiac output. Administering up to a litre fluid preoperatively in minor surgery seems to reduce postoperative drowsiness and thirst and may therefore seem appropriate [67].

It is normal to use surrogate parameters such as hourly urinary output, blood pressure or heart rate to estimate fluid balance and guide fluid therapy. However, these are normally poor indicators of fluid load.

Meta-analyses on the impact of different perioperative fluid administration schemes show mixed results. The most common interventions are goal directed fluid therapy or flow optimisation versus standard care. Most of the studies show a positive impact on some outcome measures in the interventional group compared to standard therapy [19, 68-73]. However, there is a vast variation in complication reporting in all included studies and this heterogeneity makes interpretation of the analysis difficult [70].

A Cochrane Review from 2013 included 31 studies and focused on increasing perioperative blood flow as a goal in the treatment arm [19]. There were no differences in mortality between the control and intervention group in the longest reported follow up of all 31 studies. The overall mortality was 8.9% in the intervention group vs. 10.8% in the control group,  $p=0.18$ . The authors could demonstrate a reduced complication rate regarding renal failure, respiratory failure and wound infections. Hospital length of stay was reduced by 1.16 days in the intervention group. The authors conclude that the intervention unlikely causes harm but due to the heterogeneity of outcome reporting the evidence does not support widespread implementation of goal directed fluid therapy [19].

Most studies do not examine a single clearly defined intervention. They study rather a complex care pathway, e.g.: monitor type, fluids, goals, postoperative environment and

inotropes. This heterogeneity in studies precludes a meaningful analysis of the data and diminishes the generalizability of meta-analyses.

In the current debate on which is the best method to optimize hemodynamics during surgery many questions are unanswered [64, 74]. Among these:

Firstly: Which monitoring system should be used to measure fluid load in the patient and how should fluid deficit be detected in a timely manner during surgery? [75-77]

Secondly: What is the goal in goal-directed fluid therapy? Should fluid be given in a restrictive way, in a liberal way or until a predefined threshold is met [78-82]?

Thirdly: Which is the optimal fluid to use for substitution of intravasal fluid losses [83-85]?

In summary, there is a need to evaluate the effect of goal-directed fluid therapy in the surgical population. There are many monitors that can be used to guide fluid therapy [86-92], and ScvO<sub>2</sub> as an indirect measure for cardiac output is a promising candidate.

### **1.5.10 Process change**

One may question the effect on outcome by changing one single intervention during the entire perioperative pathway. Most effect in outcome improvement may be achieved by changing and optimizing the whole perioperative process. One method to accomplish this may be to implement a program that improves the whole process of perioperative care as for example the ERAS program [93, 94] or an improved perioperative pathway planning as being proposed by the Royal College of Anaesthetists in the UK [95]. The problem in changing many factors in perioperative care at the same time would then be the inability to determine which factor has an effect.

## **2. Aims**

The overall aim of this thesis is twofold:

1. To study perioperative complications and outcome after major surgery
2. To contribute to finding ways to reduce complications after major surgery

Paper one and two in this thesis relate to the first aim, and paper three and four to the second aim.

### **Paper I:**

The aim of this paper was to create standard definitions of patient relevant clinical outcome measures for use in perioperative medicine research. The paper was designed to be applicable for large clinical trials in perioperative medicine.

Up until now there has been no consensus on how to assess complications, outcome, quality of life or mortality after surgery. Also, there is no consensus on the optimal time period over which to assess clinical outcomes.

### **Paper II:**

The aim of this paper was to provide intra-hospital mortality outcome data of patients undergoing non-cardiac surgery across Europe.

Little is known about the outcome of patients undergoing non-cardiac surgery. Outcome may vary between nations. There is an increasing recognition that even small improvements in perioperative care may have a huge potential impact on outcome, given the large number of operations annually. Implementing policy change in perioperative must be based on robust and powerful data.

### **Paper III:**

The aim of this paper was to describe the prevalence of surgical checklist use in Europe and to identify a possible relationship between surgical checklist use and mortality. There is a wide variation in implementation of surgical checklist between different health systems and between nations. There exists no epidemiologic study to evaluate the use and effect of a surgical checklist.

### **Paper IV:**

The aim of this paper was to determine the effect on outcome of fluid therapy guided preoperatively by ScvO<sub>2</sub> compared to a traditional fluid scheme in patients undergoing major abdominal surgery.

The optimal method to measure fluid load and the best approach to guide fluid therapy in major surgery is debated. Central venous oxygen saturation (ScvO<sub>2</sub>) has been used to guide fluid therapy with improved outcome in intensivecare patients.

### 3. Material and Methods

#### 3.1 Paper I: European Perioperative Clinical Outcome (EPCO) definitions

Members from the European Society of Intensive Care Medicine (ESICM) and the European Society of Anaesthesia (ESA) created a task force with the goal to work out a set of definitions for perioperative clinical outcomes.

It was emphasized that the objective was to provide a standard of definitions that could be used in large pragmatic clinical trials to evaluate outcome after surgery. There was no intention to deliver an exhaustive list of all possible outcome measures that may occur in the perioperative period. A list of events for which a definition was important, was defined *a priori*.

A literature review was conducted to assess the current state of knowledge about surgical outcome definitions. An electronic search of the PubMed database was performed on 23<sup>rd</sup> January 2013. The following search string was used to identify relevant papers:

*"Perioperative Period"[Mesh] AND ("Postoperative Complications"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Morbidity"[Mesh])*

All papers related to research on humans, written in English, French or German where included.

Non-relevant articles were screened and excluded by title; the remaining papers were reviewed by abstract. Full text was acquired for selected papers.

Key opinion leaders and members of both societies were invited to send in all relevant publications they found. Final appraisal of full-text versions of selected papers were performed by all task-force members and the final list of definitions were selected in a face-to-face meeting.



Before the literature research was conducted, the group agreed on important and relevant outcome events that should be included. When there were several valid definitions of an outcome measure, the taskforce reached a consensus on the best candidate. References to alternative definitions were inserted in the final list.

The final manuscript was sent to international key opinion leaders for input and comments before publication.

## 3.2 Paper II: European Surgical Outcome Study (EuSOS)

In April 2011 a 7 day cohort study was conducted in 498 hospitals across 28 European countries. All patients aged  $\geq 16$  undergoing non-cardiac surgery were included, except patients undergoing planned day-case surgery, neurosurgery, radiological or obstetrics procedures.

The study was funded by the ESA and ESICM. The core research group was based in London. My task was both a local investigator at Haukeland University Hospital and the national coordinator for Norway.

### 3.2.1 Ethic and regulatory requirements

This was a non-interventional study on prospectively registered patients. Data routinely collected in day-to-day care were recorded in a special case report form. Patient data were anonymized, then issued a unique EuSOS patient ID and finally uploaded to a secured internet-based electronic case record form (OpenClinica, Boston, MA, USA). All clinical data on the database was made anonymous by detaching patient identification from the case-report-form and adding a EuSOS patient ID.

The study was approved by the Regional Committee for Medical and Health Research Ethics – West as a clinical audit study and the privacy ombudsman consented in transport of anonymous data to the central research server. Paper based electronic case forms containing patient data were stored locally in a locked compartment.

Other European countries required formal ethics approval. These were applied for and given. As an exception was Finland alone required obtaining written informed consent from individual patients.

### 3.2.2 Data collecting and analysis

Patient data were registered by the treating physician on the day of surgery. An operation theatre case record form followed the patient until hospital discharge; see Figure 6 in Chapter 9. In case of transferral to an intensive care unit an intensive case

report form was completed, describing the first intensive care admission. Patient data was censored 60 days after surgery. The primary endpoint was in-hospital mortality with duration of hospital stay and admission to critical care as secondary outcome measures.

For statistical analysis plan see Paper II. A list of participating hospitals can be found in the supplementary appendix:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3493988/bin/mmc1.pdf>

### 3.3 Paper III: Point prevalence of surgical checklist use in Europe

To assess the prevalence of checklist use in Europe, a secondary analysis of the EuSOS data set was performed. One item on the case report form of the EuSOS study was whether a checklist was used during the per-operative period of each individual patient. No other details like type of checklist or how the checklist was used were recorded.

For quality improvement, the primary analysis was performed of a data set that excluded sites above the 95<sup>th</sup> centile for mortality and sites that contributed with  $\leq 10$  patients.

The primary outcome was defined as in-hospital mortality within 60 days of surgery. For statistical analysis plan, see paper III.

### 3.4 Paper IV: Goal directed fluid therapy in colorectal surgery

In this study we evaluated the influence of per-operative ScvO<sub>2</sub> guided fluid therapy on postoperative outcome. All patients undergoing elective colorectal surgery in two participating hospitals were screened consecutively for eligibility. Patients were randomized into two groups. The control group received traditional fluid therapy; the intervention group received a goal-directed fluid approach guided by ScvO<sub>2</sub>.

We chose a threshold for ScvO<sub>2</sub> ≥ 75% based on known physiologic data [96-98]. Fluid in the ScvO<sub>2</sub>-group was given following an algorithm (Figure 2). The control group received protocol-based fluid after a more traditional scheme based on weight, urinary output, blood pressure, the amount of bleeding and the anaesthesiologist discretion. The ScvO<sub>2</sub> group got low crystalloid maintenance and additional boluses with hydroxyethyl starch. The control group got effluent crystalloids. Hydroxyethyl starch was given as blood loss compensation in both groups.

Written and informed consent was obtained from all included patients. The study was approved by the Regional Committee for Medical Research Ethics – West.

The primary endpoint of the study was postoperative complication rate within 30 days after surgery. A predefined list of complications was filed by an assessor blinded surgeon during follow up 4-6 weeks after surgery.

For statistical analysis plan and the predefined list of complication, see Paper IV.

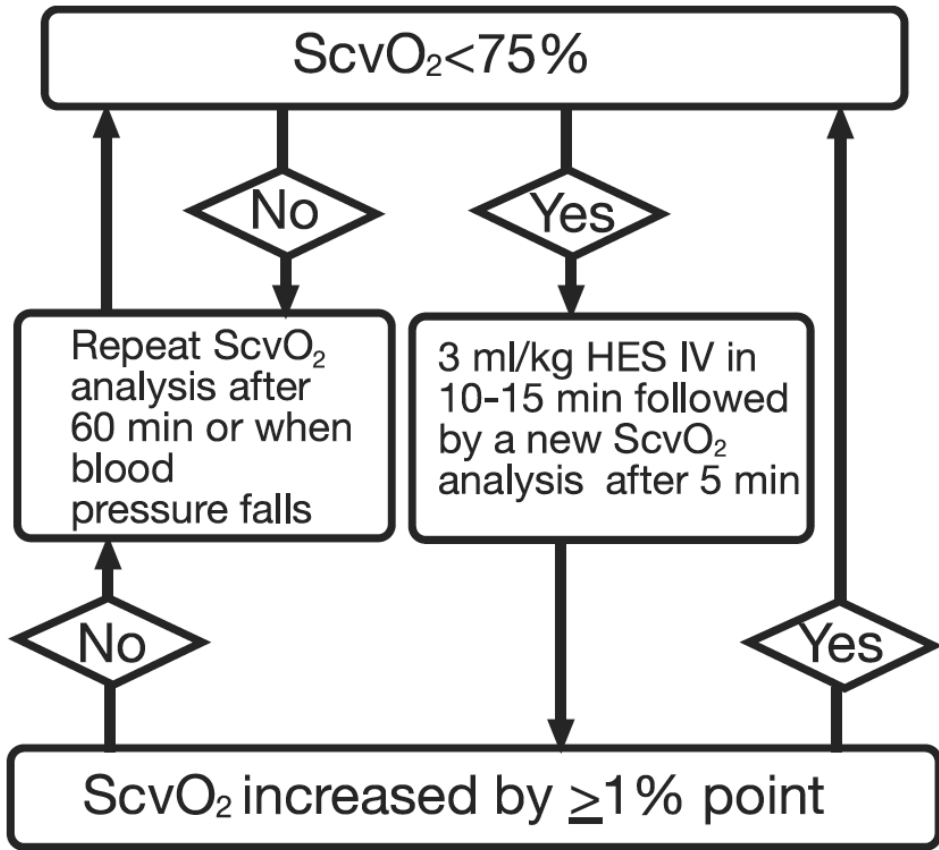


Figure 2: Fluid algorithm for the ScvO<sub>2</sub> group. HES = hydroxyethyl starch; ScvO<sub>2</sub> = central venous oxygen saturation.

## 4. Synopsis of Results

### 4.1 Paper I: European Perioperative Clinical Outcome (EPCO) definitions

The literature search and the open call for papers resulted in 11.666 papers to assess. Most papers were excluded by title or abstract screening. For the final analysis we included 33 articles. The flow of the literature through the review process can be seen in Figure 3.

Paper I describes the outcome measures organized in four different categories:

1. Individual adverse events

A total of 22 individual adverse events were described. Each event includes a severity grading. In events where one or more valid alternative definitions could be identified, we reached a consensus on the best candidate, but included references to alternatives.

2. Composite outcomes

Four composite outcome measures were identified, focusing on specific outcome categories. These were major adverse cardiac events, pulmonary complications or a combination of different postoperative morbidity items.

3. Grading of complications

Severity grading of outcome measures are important, because they may vary widely. We therefore adopted a simple system where grading was not an integral part of the definition. The important feature of the grading is that they do not define severity according to medical or surgical treatment. However, if this is not a concern, the Clavien-Dindo grading system may be preferable [28].

#### 4. Health related quality of life (HRQL)

Quality of life measures were identified but no one had been specifically designed to examine quality of life after surgery. However, the four measures identified are well validated tools to assess quality of life in different level of detail.

In addition we identified the best practice in duration of follow up period.



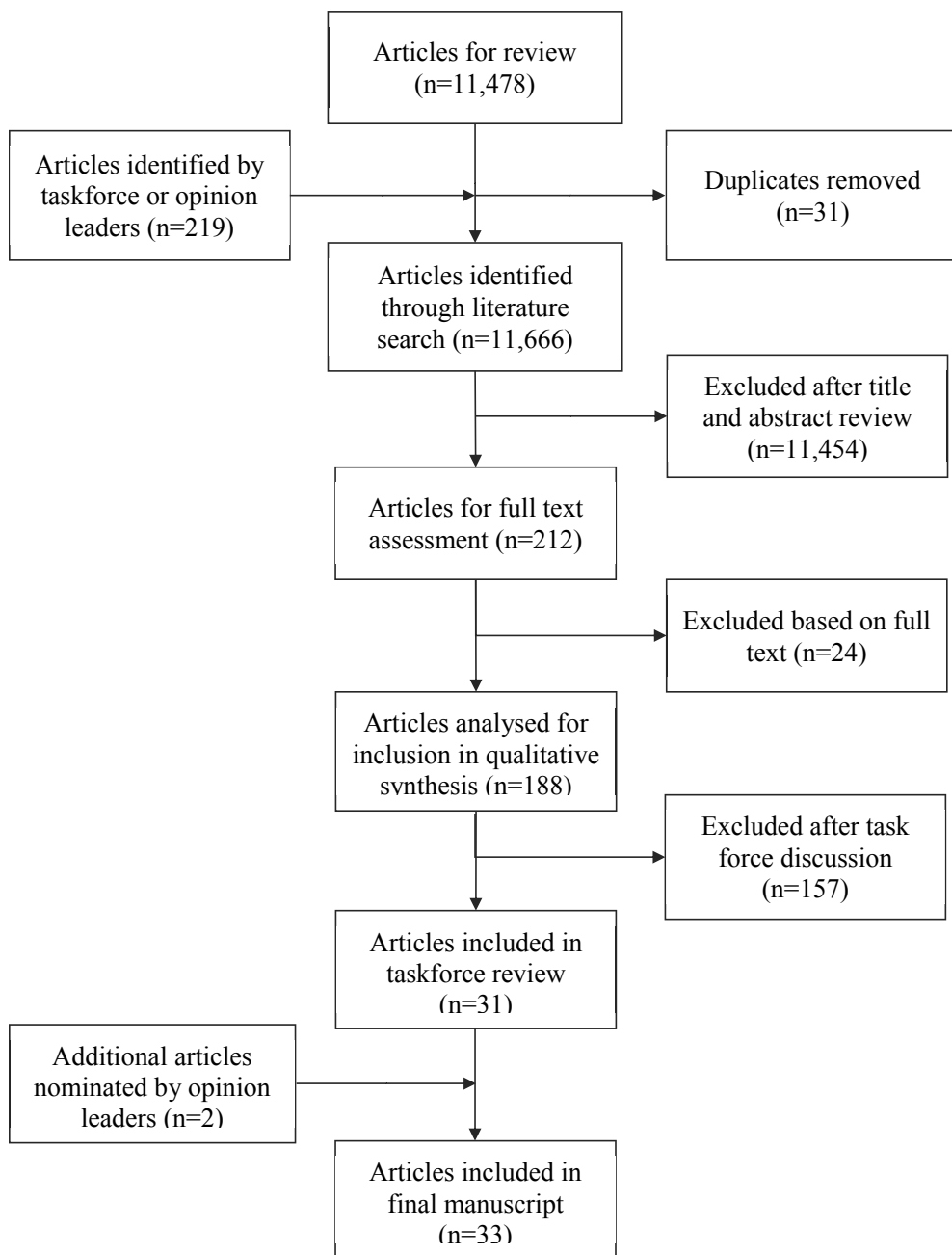


Figure 3: Flowchart of literature review process

## 4.2 Paper II: European Surgical Outcome Study (EuSOS)

A total of 498 hospitals in 28 European nations participated in the study, including 46539 patients for analysis. The overall crude intra-hospital mortality was 4%. The prevalence of crude mortality differed substantially between countries (Figure 4) with high mortality rates in Poland, Latvia, Romania and Ireland when using the UK as a reference.

In 1358 of the patients who died (73% of all deaths) no admittance to an intensive care unit at any stage after surgery was performed.

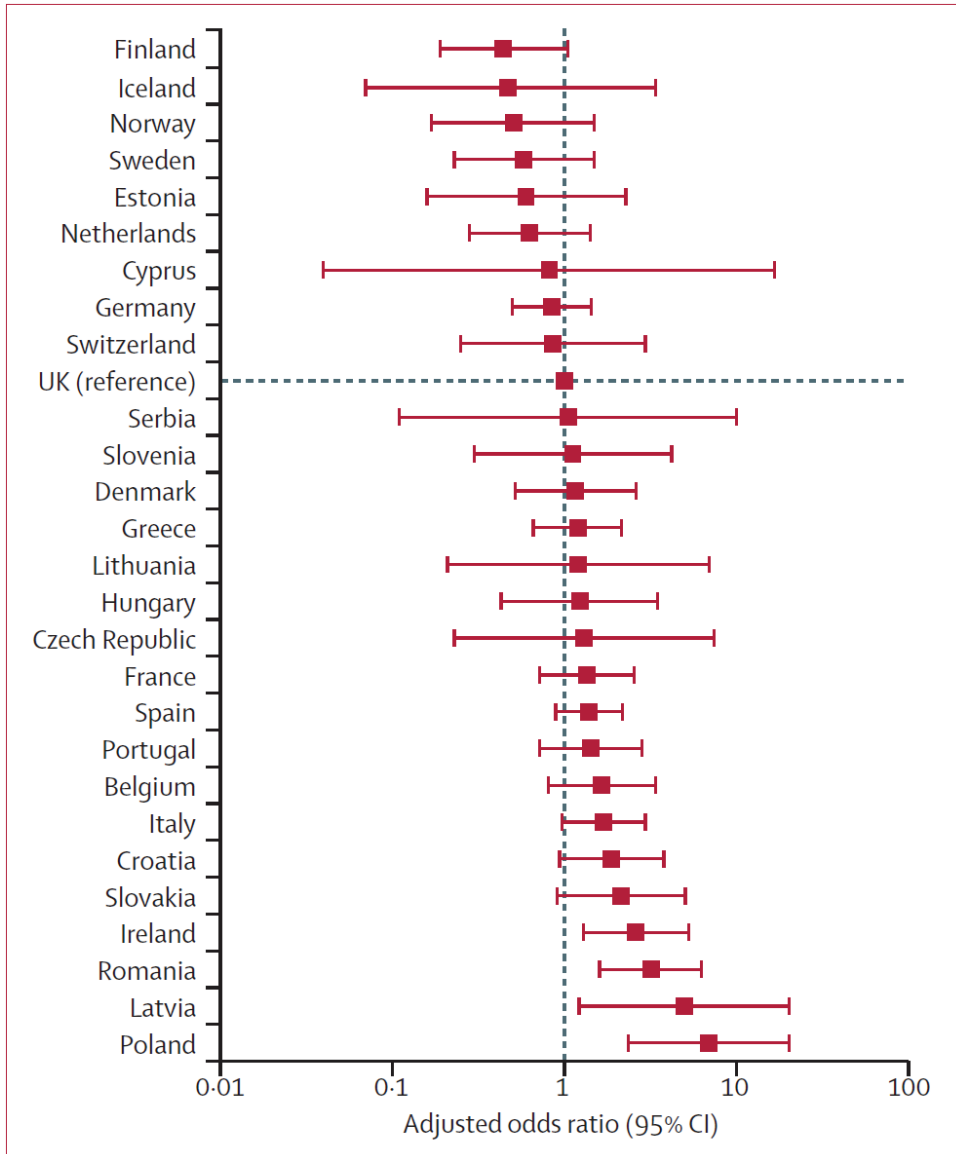


Figure 4: Adjusted odds ratio for intra-hospital death after surgery for each participating country.

### 4.3 Paper III: Point prevalence of surgical checklist use in Europe

Of 46539 patients in the EuSOS data base, 45591 were included in the primary analysis after excluding outlier hospitals above the 95th centile for mortality and hospitals recruiting  $\leq 10$  patients. The prevalence of checklist use in this population was 67.5%. However, there was a marked variation in checklist use and mortality rates in individual countries.

- The mortality in the group where a surgical checklist was used was 2.80%.
- The mortality in the group where no surgical checklist was used was 3.33%.
- The overall mortality of the cohort included in the primary analysis was 3.0%.
- The use of a surgical checklist was associated with a lower hospital mortality (OR 0.84, CI 0.75–0.94; P=0.002).

When adjusted for baseline risk factors in a multivariate regression model, the effect of a surgical checklist on mortality was stronger (OR 0.81, CI 0.70–0.94; P=0.005).

Mortality after surgery increases with more urgent procedures. The protective effect of the surgical checklist remains, regardless of urgency (Table 1).

Urgency of surgery	Checklist use	Mortality for patients not exposed to surgical checklist	Mortality for patients exposed to surgical checklist
Elective	66.6%	247 (2.2%)	479 (2.1%)
Urgent	70.2%	152 (5.9%)	249 (4.1%)
Emergency	70.2%	94 (12.6%)	134 (7.6%)

*Table 1: Comparison of mortality for patients exposed to a surgical checklist according to urgency of surgery. Data presented as n(%).*

### 4.4 Paper IV: Goal directed fluid therapy in colorectal surgery

During two years 403 patients were assessed for eligibility and 241 of them were included in the study. All randomized patient groups were analysed based on intention to treat. For the patient flow through the trial see Figure 5.

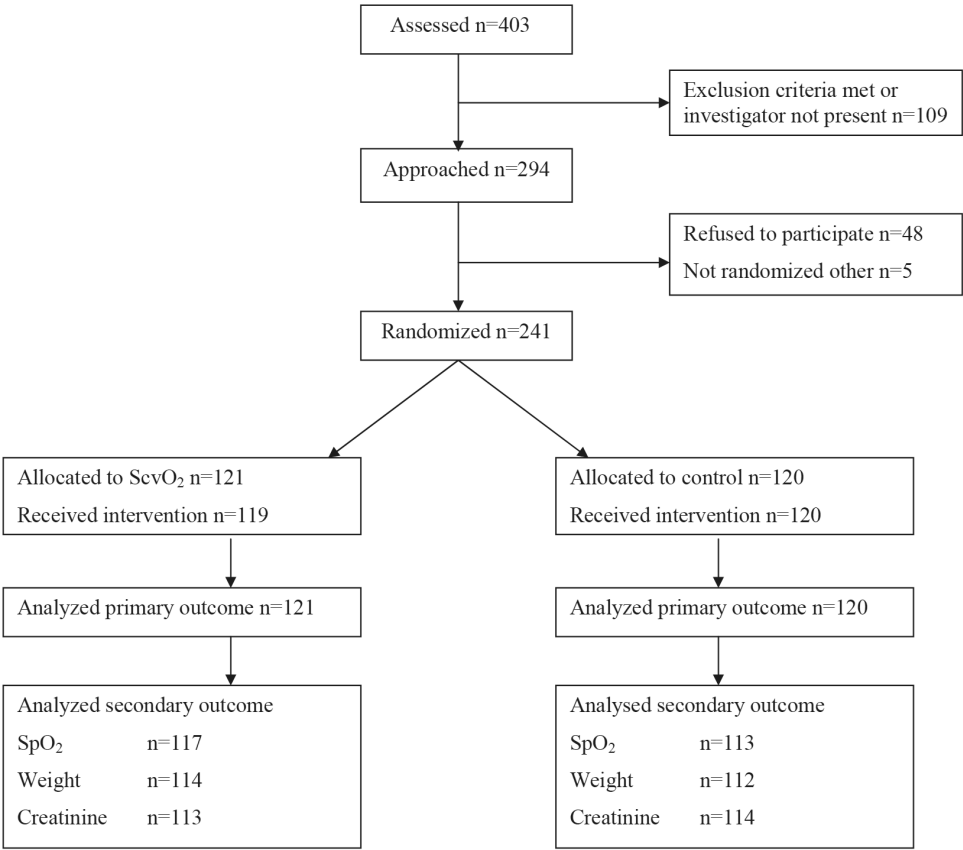


Figure 5: Flow chart for patients' progression through the trial. ScvO2=central venous oxygen saturation; SpO2=pulse oximetry saturation.

There was a difference in the amount of fluid given until 8am the next morning. The ScvO<sub>2</sub>-group received less fluid compared to the control group (3869±992ml vs. 6491±1649ml, p<0.01). The complication rate 30 days after surgery was equal in both groups (Table 2).

	ScvO <sub>2</sub> group	Control group
Amount of patients	121	120
Sum of complications	114	112
<b>Patients with at least one complication</b>	<b>51(42%)</b>	<b>51(42%)</b>

*Table 2: Amount of complications in both study groups. Data presented as n(%).*

## **5. Discussion**

### **5.1 Paper I: European Perioperative Clinical Outcome (EPCO) definitions**

Postoperative complication registration is important to adequately audit and compare the quality of care in the perioperative period. It is also important in clinical trials. A paper from 2015 reports that in the three major surgical Journals (Annals of Surgery, JAMA Surgery and British Journal of Surgery) half of the published randomized controlled trials did not use exact definitions of postoperative complications. The papers that provided a classification of postoperative complications, mostly used a severity scoring [99].

Only when both the complication itself and the severity of that complication are registered in a uniform way, a meaningful comparison of quality of care and of clinical trials can be done [100].

To fulfil this need, we proposed a standard of outcome measures in perioperative medicine research and clinical audit. The focus was on the most important and relevant outcomes that could occur in a mixed surgical population, and which are relevant to perioperative outcome research. The outcome measures listed are thus not a comprehensive list of all possible outcomes that may occur.

#### **5.1.1 Identification of relevant papers**

It was obvious that the area of perioperative medicine research is relatively new. There exists no Medical Subject Heading (MeSH) term to identify relevant perioperative medicine research articles.

Even with comprehensive PubMed search and co-operation with key opinion leaders in perioperative medicine, we cannot exclude that we have missed some relevant papers from outside our research community.

It was not possible to find a satisfactory definition for some outcome measures. For example, there is a wide variation in the literature about the definition of paralytic ileus [101]. This makes it challenging to find a good definition that can be agreed on. Similar for the definition of anastomotic breakdown: a systematic review published in 2001 found 56 different definitions based on 97 studies [102]. None of the studies used the standard definition that ten years earlier was proposed at a consensus workshop [103], and which is chosen in our list.

### **5.1.2 Duration of follow up**

Adverse events after surgery are often reported up to 30 days. However, 30 day mortality is not an adequate end-point of patient-centred clinical-effectiveness studies. Many patients who develop severe complications may die after the 30 days observational period [9, 104]. For patients it may be more relevant to know the expected quality of life and functional status after surgery. Also 30 day outcome is a too short timeframe to evaluate health related quality of life and physical status since most rehabilitation periods are longer.

### **5.1.3 Registration of data in outcome research**

Validity check of the data collected is important in database building. Residents are often mandated to record surgical outcomes without proper training and dedicated time for this activity, and may therefore lack motivation for collecting reliable data. Hence, when reporting outcome data, the most complete and correct data set can, not surprisingly, be obtained with dedicated personal [105].

When generating data for outcome research, data integrity is important to ensure a reliable database. Two approaches can preserve data integrity [106]:

- 1) Quality assurance: actions that take place before data collection begins, e.g. training of staff and standardisation of listed items.
- 2) Quality control: actions that take place during and after data collection, e.g. review of data to identify inconsistencies, spot checks and continuing staff training.



Room for interpretation when recording outcome should be avoided. Registration of an outcome should not be based on treatment decisions, e.g. defining pneumonia when the treating physician starts antibiotic therapy against an assumed pneumonia. This would open up for a wide interpretation of the outcome. As a consequence, training of physicians is essential. This aids to a uniform classifying of events and avoids unreliable data [107].

## 5.2 Paper II: European Surgical Outcome Study (EuSOS)

The study confirms a variation in outcome after surgery in European countries, with adjusted odds ratio for mortality varying from 0.44 to 6.92 with the UK as a reference. This could indicate that there is divergence in the standard of care.

Identification of key factors in perioperative care and subsequent improvement and standardisation within the care pathway could therefore improve postoperative outcome throughout Europe.

Similar data can be found within the UK. A study found a variation in operative and anaesthetic care as well as in postoperative pathways leading to a variation of intra-hospital mortality in emergency laparotomy patients [108].

Interestingly, in our study 1358 patients died (73% of all deaths) without being admitted to an intensive care unit at any stage after surgery. This raises the question if postoperative admission to an intensive care unit can prevent unfavourable outcomes [109]. There is a large variation in the numbers of intensive care beds in Europe [110, 111]. The availability of ICU beds did however not seem to explain why so many patients died without being admitted to an ICU. The Nordic countries, for example, have a low number of ICU beds compared to the rest of Europe [111], but have a low postoperative intra-hospital mortality. A more plausible explanation may be differences in selection of patients who are accepted for surgery as well as political, cultural, socioeconomic and demographic differences between nations. All these factors might affect population health and health-care outcomes. Admitting many more postoperative patients to an intensive care unit would possibly overwhelm most health systems. The correct identification of patients that would benefit from postoperative intensive care treatment is therefore crucial.

Our study on mortality after non-cardiac surgery in Europe has been widely debated [112-119]. The validity of the database has been questioned, especially from countries with a high intra-hospital mortality rate. Recalculations of the cohort, excluding

outliers over 95<sup>th</sup> centile for mortality and centres including ten patients or less during the study period, resulted in a reduction of the overall mortality from 4% to 3% [117].

However, the main message of this paper remains: overall mortality was previously estimated to be 1-2% [2, 7, 104, 120], but is significantly higher in reality. There is a large variation in postoperative mortality across different health systems. The high number of deaths in patients that did not receive intensive care treatment suggests a failure in recognition and identification of patients who could benefit from such treatment.

Standardizing the postoperative care pathway for non-cardiac surgical patients could therefore improve survival similar to the cardio-thoracic surgical population that receives a defined and more standardized care after surgery.

## 5.3 Paper III: Point prevalence of surgical checklist use in Europe

Checklists were used systematically first in aviation. Introduction of a checklist resulted in a change in communication culture and broke down the complexity of actions [58]. Strict hierarchy in the cockpit as well as in the operation theatre prevents constructive feedback and is prone to undiscovered errors. Hierarchy may therefore lead to an unfavourable outcome [121].

The mechanism how the use of surgical checklists improve outcome is still debated. Some authors describe the improvement of teamwork and communication as one explanation [122, 123]. The introduction of a checklist is a low cost intervention and has no adverse effect on patient outcome [124].

We found an association between checklist use and improved mortality in Europe. The checklist itself may cause improvement in survival when using it. However, it is more likely that structural factors that improve patient care already exist in hospitals that have introduced the surgical checklist. In such an environment patient safety is an important issue, communication barriers are broken down and awareness exists in the theatre team. This improves patient care and perioperative treatment, and consequently surgical outcome. Haugen et al. used a stepped wedge cluster method to introduce checklists in two hospitals. By this method bias from the control arm could be minimized. Additionally the staffs received special training via an educational program on how to use the checklist. The authors could demonstrate a decrease of complication rate from 19.9% to 11.5% with an absolute risk reduction in complication rate of 8.4 after the introduction of a surgical checklist [125].

There is a lack of consistency in how the checklist is used in health care systems. In Ontario they reported no statistically significant reduction in deaths or complications after a top-down implementation of a surgical checklist when analysing self-reported use of checklist [126]. The findings of this study and its accompanying editorial [127] were debated [128-132]. It was emphasized that a checklist implementation process may only be successful with a simultaneous culture change. One comment pointed out

a methodological weakness: The authors failed to compare the self-reported compliance to the actual checklist use. This is also a weakness of Paper III: checklist use was documented on a patient case report form, but what type of checklist was used was not asked and the data was not validated in any way other than self-reporting.

A checklist is not always carried out to its intention and compliance to checklist adherence varies. Although it may be documented as complete in administrative data, the real use may be inaccurate and divert greatly from recorded data [133-136]. The data is especially unreliable when self-reported compliance is recorded using an electronic format [136]. This questions research on checklist use based on administrative data and can explain variations in outcome between studies evaluating the effect of checklists [134]. Adherence to a checklist may deviate from the reported compliance [137].

The introduction of a checklist in a complex environment as the operation theatre could make the staff feel jeopardized in their independence and motivate to misleading reporting on the actual use [138]. A government mandated or hospital top-down introduction of a checklist may therefore result in a good self-reported compliance without a real behavioural change.

A successful implementation of a clinical intervention is highly dependent on an environment that welcomes the change in routines and of a continuous facilitation and promotion [139]. A decreased surgical mortality is associated with improved team culture and checklist introduction that trigger operation room briefings and decrease communication thresholds as demonstrated by Neily et al. [140]. They investigated more than just checklist implementation. A part of the intervention was ongoing coaching, training of teamwork competences and creating a support network. The teams were not forced to just tick off items on a list, they were encouraged to use a list as a tool to strengthen and boost communication. The focus on checklist implementation alone may distract the focus from how to really achieve safer care. Keeping attention on checklist use may be an oversimplification. A more important factor than checklist use in improving outcome may therefore be a change in

sociocultural behaviour between health care workers by rejecting the command and control regime [141, 142].

In contrast, researchers could not affect surgical outcome after introducing a checklist based quality program in a study including >64.000 patients from 14 participating centres in Michigan, USA [143]. The authors suspected a failure since their program was implemented in the operation room; in a heterogeneous group involving complex procedures and frequently changing personnel. They suspect that such a complex environment is less susceptible for change. This may have complicated their successful implementation across the whole organisation [143].

A meta-analysis examining the effect of the WHO surgical safety checklist reported an association between checklist use and improved outcome [144]. However, the studies included in this review were heterogeneous and showed mixed results. Also, no study used a control group that may identify a coincident trend toward improved outcome occurring during the study period. As an example a study from the UK demonstrated an improved outcome during the Health Foundation's Safer Patient Initiative, however, the effect was not bigger than the improvement seen in control hospitals during that period [145].

We should not forget that checklists are just simple reminders of what to do. They need to be connected to a change of attitude within the health care team. If this is not facilitated, checklists may not have an impact.

## 5.4 Paper IV: Goal directed fluid therapy in colorectal surgery

In a goal-directed approach, fluid is given as a bolus to see if stroke volume increases, indicating a preload reserve. In that case it also indicates that the patient is fluid responsive and in need of fluid resuscitation to improve circulation. A fluid bolus may then be repeated until there is no or minimal increase in stroke volume, indicating maximization of stroke volume and cardiac output [146]. There are several tests that may predict if a fluid challenge leads to increased stroke volume:

- Passive leg rising by auto infusion of blood from the lower extremities and observing a response in blood pressure rise.
- Measuring stroke volume variation (SVV) and pulse pressure variation (PPV) by an arterial line.
- Using Oesophagus Doppler to measure stroke volume. This has been recommended by the National Institute for Health and Clinical Excellence (NICE) [147] and has been vigorously criticised and discussed since its introduction [148-156].

There is no common definition of what is “liberal”, “standard” or “restricted” fluid therapy in studies comparing different fluid regimen, and comparison of these trials in meta-analyses is therefore problematic.

Fluid maintenance and replacement per hour is calculated by the weight of the patient and the extent of the surgery [157]. For major surgery the textbook of Morgan and Mikhail’s Clinical Anaesthesiology describes an additional hourly fluid requirement up to eight ml/kg on top of maintenance fluid to compensate for redistribution and evaporative surgical fluid losses [157]. This may add up to 1000 ml fluid per hour for the patient. A resultant weight gain of more than three kg postoperatively due to fluid overload is typical [158]. Although these are established guidelines, it is generally perceived that this calculated approach may lead to overhydration and consequently altering outcome [159, 160].

In our study 89% of the patients were ASA class I or II and hence relatively healthy. This patient group has still a good hemodynamic buffer reserve and is therefore less prone to complications after hypovolemia. This may have contributed to the finding of no difference in outcome between the study groups, despite the difference in the amount of fluid both groups received. The patient group that may benefit most from a goal-directed fluid therapy is the patient with the highest risk of a postoperative complication [161]. These patients have lost the ability to compensate hemodynamically for the perioperative stress and impact. As a consequence they are not able to meet the oxygen transport demands during the perioperative period, exposing them to a higher risk for complication and death.

Goal-directed fluid therapy in the perioperative care pathway is costly. Health personnel need to be trained and investment in equipment is needed. But as a result patients at high risk may have fewer complications, thus avoiding critical-care treatment or a longer hospital length of stay. Research in this area is therefore presumably cost effective [162-164].

Central venous pressure has been used for over 50 years to guide fluid therapy [165]. However, central venous pressure should not be used to guide fluid therapy or as a goal for fluid resuscitation [166].

Central venous oxygenation ( $ScvO_2$ ) refers to the haemoglobin oxygen saturation in the superior vena cava [167] and can be used as an indirect marker of oxygen delivery ( $DO_2$ ). Adjusting  $DO_2$  to oxygen consumption has been associated with a decreased complication rate and therefore assumed that  $ScvO_2$  may be a promising measure [168].

A low  $ScvO_2$  in the perioperative phase is associated with an increased risk of postoperative complications. Therefore  $ScvO_2$  seems to be a good measure to guide fluid therapy [96] and maximization should be the goal [169, 170]. There is a correlation between  $ScvO_2$  concentration and systemic oxygen delivery ( $DO_2$ ),



indicating that ScvO<sub>2</sub> can be used as a surrogate to increase DO<sub>2</sub>, estimate cardiac output and guide fluid load [171-174]. Fluctuations in ScvO<sub>2</sub> after surgery is associated with increased post-operative complications. Therefore it has been suggested to evaluate how per-operative ScvO<sub>2</sub> influences postoperative outcome [97, 175].

We used ScvO<sub>2</sub> to guide fluid therapy as a surrogate for cardiac output. As ScvO<sub>2</sub> reflects the balance between oxygen delivery and oxygen consumption, it is affected by a wide range of factors in the perioperative period and not only fluid load. Common factors that affect oxygen delivery are for example hypoxia, anemia, hypovolemia, inotropic agents, O<sub>2</sub>-therapy and blood transfusion. Oxygen consumption is affected by pain, agitation, fever, shivering, anaesthesia, warming, respiratory support and sedation [98, 173]. It has been suggested that a per-operative supra-normal oxygen supply would increase oxygen delivery and hence decrease postoperative complication rate in form of surgical site infection. This could not be confirmed in a trial including 1400 patients undergoing laparotomy and comparing FiO<sub>2</sub>=30% with FiO<sub>2</sub>=80% [176].

In an early sepsis trial from 2001, a ScvO<sub>2</sub>-guided goal directed fluid approach resulted in a reduction of in-hospital mortality from 46.5% to 30.5%. The control group received a fluid therapy guided by central venous pressure, mean arterial pressure and urinary output while the intervention group received fluid guided by ScvO<sub>2</sub> [177]. However, in our study goal directed fluid therapy guided by ScvO<sub>2</sub> had no impact on outcome. This lack of effect in ScvO<sub>2</sub> guided fluid therapy on outcome was recently confirmed in three trials including patients in early septic shock [178-180].

## 6. Conclusions

Paper I:

- Standards for outcome measures are proposed. These can be used in perioperative medicine research and clinical audit. This could contribute to high-quality research methodologies within perioperative research.

Paper II:

- The intra-hospital mortality rate in Europe after non-cardiac surgery is higher than previously anticipated.
- There is a wide variation in mortality between different health care systems.
- This variation indicates variations in care pathways and a clear potential to improve outcome in this patient group.

Paper III:

- Surgical checklist use is associated with lower hospital mortality in a mixed surgical population.
- This observation may indicate a protective effect of the checklist itself or may be an indicator of an increased quality of perioperative care.

Paper IV:

- Patients undergoing colorectal surgery with a goal directed fluid approach guided by ScvO<sub>2</sub> have no different outcome compared to patients treated with a traditional fluid approach.

## **7. Future Research**

Future trials investigating postoperative complications will hopefully use the standardized outcome measures in perioperative medicine developed in paper I. The foundation of national and international perioperative registers would also help to establish a greater research community in perioperative outcome research. These registers can assist to identify factors in the perioperative care pathway that improve outcome.

It is not likely that one single intervention in the perioperative period will markedly affect outcome. A multifactorial intervention is most likely to be successful in reaching this goal. However, specific research in the high-risk surgical population is lacking. It can be assumed that this patient group would have the greatest benefit from an improved perioperative care pathway.

## 8. Abbreviations

CPAP	Continuous positive airway pressure
DO <sub>2</sub>	Systemic oxygen delivery
DVT	Deep vein thrombosis
EPCO definitions	European Perioperative Clinical Outcome definitions
ERAS	Enhanced recovery after surgery
ESA	European Society of Anaesthesia
ESICM	European Society of Intensive Care Medicine
EuSOS	European Surgical Outcome Study
FiO <sub>2</sub>	Fraction of inspired Oxygen
HFNC	High-flow nasal cannula
HRQL	Health related quality of life
LOS	Length of stay
MeSH	Medical Subject Heading
NICE	National Institute for Health and Clinical Excellence
NSQIP	National Surgical Quality Improvement Program
POMS	PostOperative Morbidity Survey
PPV	Pulse Pressure Variation
ScvO <sub>2</sub>	Central venous oxygen saturation
SVV	Stroke Volume Variation
UK	United Kingdom
WHO	World Health Organisation



Patient EuSOS ID code

**Most senior anaesthetist present in operating room**

Attending       Middle Grade       Junior (<3 years in anaesthesia)

**Most senior surgeon present in operating room**

Attending       Middle Grade       Junior (<3 years in surgery)

Intra-abdominal surgery       Y       N

Intra-thoracic surgery       Y       N

Laparoscopic surgery       Y       N

Laparoscopic assisted surgery       Y       N

Central venous catheter inserted?       Y       N

**Cardiac output monitoring during surgery?**

Doppler ultrasound       Arterial wave form analysis

Pulmonary artery catheter       Other       None

Urgency of surgery:       Elective       Urgent       Emergency

Severity of surgery:       Minor       Major       Intermediate

Blood loss during surgery:      ml

End of surgery time & date:   :

**Post-operative Follow Up**

Duration of post-anaesthetic recovery stay   :

Invasive ventilation within 24 hrs of surgery       Y       N

Non-invasive ventilation within 24 hrs of surgery       Y       N

Inotrope / vasopressor infusion within 24 hrs of surgery       Y       N

Survival to hospital discharge?       Y       N

Date of hospital discharge (or death):

Critical care admission any time during hospital stay?       Y       N

Figure 6: Operation room case report form for the EuSOS study.

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