The provision of optimal sedation in critically ill patients who are mechanically ventilated is pivotal to patient comfort, safety and survival. Whether optimal sedation is achieved may be determined by the choice of sedative agents, the intensity of sedation delivered, and the interaction of these choices with the concurrent critical illness and pre-existing comorbidities.

The impact of sedative drug choice, midazolam versus propofol versus dexmedetomidine, on sedation-related outcomes has been assessed in previous randomised trials. Different strategies designed to optimise the intensity of sedation delivered have also been investigated, aiming to reduce unwarranted deep sedation. These studies have advanced our knowledge and practice; however, these interventions were delivered in isolation, either with sedative agents compared in the absence of detailed protocols, or with comparisons of depth-of-sedation protocols that did not specify the sedative agents. In addition, these trials did not examine patient-centred outcomes such as long term mortality, as well as functional and cognitive status after the intensive care unit stay.

We have previously identified a significant independent association between the depth of sedation in the first 48 hours after the initiation of mechanical ventilation and the risk of death at 6 months in critically ill patients ventilated for more than 24 hours. Therefore, we proposed a combination strategy, where sedative agents and a targeted sedation algorithm are combined and delivered soon after initiation of mechanical ventilation, named “early goal-directed sedation” (EGDS). This concept was tested in a pilot randomised trial which confirmed the feasibility of this approach. The Sedation Practices in Intensive Care Evaluation (SPICE) III study is designed to compare EGDS, using dexmedetomidine as a primary sedative, with standard care in critically ill patients who are expected to require mechanical ventilation for more than 24 hours.

SPICE III is conducted on behalf of and endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, managed by the Australian and New Zealand Intensive Care Research Centre at Monash University, and funded by the National Health and Medical Research Council of Australia (project grant no. 1043938), the Health Research Council of New Zealand (project grant no. 14/115).

ABSTRACT

Background: Sedation strategy in critically ill patients who are mechanically ventilated is influenced by patient-related factors, choice of sedative agent and the intensity or depth of sedation prescribed. The impact of sedation strategy on outcome, in particular when delivered early after initiation of mechanical ventilation, is uncertain.

Objectives: To present the protocol and analysis plan of a large randomised clinical trial investigating the effect of a sedation strategy, in critically ill patients who are mechanically ventilated, based on a protocol targeting light sedation using dexmedetomidine as the primary sedative, termed “early goal-directed sedation”, compared with usual practice.

Methods: This is a multinational randomised clinical trial in adult intensive care patients expected to require mechanical ventilation for longer than 24 hours. The main exclusion criteria include suspected or proven primary brain pathology or having already been intubated or sedated in an intensive care unit for longer than 12 hours. Randomisation occurs via a secured website with baseline stratification by site and suspected or proven sepsis. The primary outcome is 90-day all-cause mortality. Secondary outcomes include death, institutional dependency, cognitive function and health-related quality of life 180 days after randomisation, as well as delirium-free, coma-free and ventilation-free days at 28 days after randomisation. A predefined subgroup analysis will also be conducted. Analyses will be on an intention-to-treat basis and in accordance with this pre-specified analysis plan.

Conclusion: SPICE III is an ongoing large scale clinical trial. Once completed, it will inform sedation practice in critically ill patients who are ventilated.
and the National Heart Institute of Malaysia. This report presents the trial protocol and the statistical analysis plan. SPICE III is registered with clinicaltrials.gov (NCT01728558).

Methods
Study design and participants
SPICE III is a phase 3, prospective, multicentre, multinational, open-label, randomised superiority trial of EGDS compared with standard care. The study will maximise external validity by including patients admitted to ICUs in a range of hospitals across the world, such as tertiary, metropolitan, rural and regional hospitals.

Study population
Inclusion criteria
Patients must satisfy all of the following inclusion criteria:
• the patient has been intubated and is receiving mechanical ventilation;
• the treating clinician expects that the patient will remain intubated the day after tomorrow (ie, unlikely to be extubated the following day); and
• the patient requires immediate ongoing sedative medication for comfort, safety and to facilitate the delivery of life support measures.

Exclusion criteria
Patients are excluded from the study if any of criteria listed in Table 1 apply.

Randomisation
Randomisation is conducted through a secure, password-protected website using a central, computer-based randomisation program that provides immediate allocation. Balance of confounders is enhanced via stratification by site and by whether sepsis is suspected, proven or absent. Patients who satisfy all inclusion criteria and have no exclusion criteria are randomly assigned in a 1:1 ratio to either EGDS or standard care sedation, using a permuted block method with variable block sizes of 2, 4 or 6.

Study treatments and interventions
EGDS is a combination strategy (Table 2) that involves:
• the early delivery of adequate analgesia (opioid ± other analgesics) and targeted sedation using dexmedetomidine as a primary sedative shortly after initiation of mechanical ventilation;
• the titration of sedative agents to maintain Richmond Agitation–Sedation Scale (RASS) levels between –2 to +1, unless otherwise specified by the treating clinician; and
• the minimisation of benzodiazepine use.

In the standard sedation group, the choice of analgesics and sedatives is at the discretion of the treating clinician, with dexmedetomidine used only in exceptional circumstances.

Dexmedetomidine supply and distribution
In Australia and New Zealand, dexmedetomidine is provided free of charge by Pfizer Australia (formerly Hospira) and delivered to study sites by the coordinating centre. In Europe, Orion Pharma provides dexmedetomidine directly.

Table 1. Study exclusion criteria

<table>
<thead>
<tr>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 18 years</td>
</tr>
<tr>
<td>Patient is pregnant or lactating</td>
</tr>
<tr>
<td>Patient has been intubated (excluding time spent intubated within an operating theatre or transport) for &gt; 12 hours in an ICU</td>
</tr>
<tr>
<td>Proven or suspected acute primary brain lesion, such as traumatic brain injury, intracranial haemorrhage, stroke or hypoxic brain injury</td>
</tr>
<tr>
<td>Proven or suspected spinal cord injury or other pathology that may result in permanent or prolonged weakness</td>
</tr>
<tr>
<td>Admission as a consequence of a suspected or proven drug overdose or burns</td>
</tr>
<tr>
<td>Planned administration of ongoing neuromuscular blockade</td>
</tr>
<tr>
<td>MAP pressure &lt; 50 mmHg despite adequate resuscitation and vasopressor therapy at time of randomisation</td>
</tr>
<tr>
<td>Heart rate &lt; 55 beats per minute unless the patient is being treated with a β-blocker or a high grade atrioventricular block in the absence of a functioning pacemaker</td>
</tr>
<tr>
<td>Known sensitivity to any of the study medications or the constituents of propofol (eg, soya or peanut protein)</td>
</tr>
<tr>
<td>Acute fulminant hepatic failure</td>
</tr>
<tr>
<td>Patient has been receiving full-time residential nursing care</td>
</tr>
<tr>
<td>Death is deemed to be imminent or inevitable during this admission and either the attending physician, patient or substitute decision maker is not committed to active treatment</td>
</tr>
<tr>
<td>Patient has an underlying disease that makes survival to 90 days unlikely</td>
</tr>
<tr>
<td>Patient has been previously enrolled in the SPICE III study</td>
</tr>
</tbody>
</table>

ICU = intensive care unit. MAP = mean arterial blood.
to study sites. In Malaysia, dexmedetomodine is provided at a discounted commercial rate to the National Heart Institute, which distributes study medication to study sites. Partial supply of dexmedetomodine is provided by Pfizer to participating sites in Saudi Arabia. Pfizer have not otherwise been involved in the study design or conduct.

Data collection and monitoring
A purpose built and designed website with an electronic case report form (CRF) is used for data collection at participating sites. All data are collected by trained research staff at each study site directly from the clinical chart source data. Information recorded in the CRF is required to accurately reflect the participant’s medical and hospital notes.

The study timelines, procedures and assessments are shown in Table 3.

A study monitor from the Australian and New Zealand Intensive Care Research Centre is undertaking site visits at least twice during the study and on an as-needed basis to check for study compliance, accuracy and completion of data collection.

Study outcomes
Primary outcome
The primary outcome of this study is death from all causes at Day 90 after randomisation. Study outcomes are presented in Table 4.

Statistical plan
Sample size
The sample size for this study has been calculated based on the mortality rate of 26% observed in our previously published study.11 A study population of 4000 patients will provide 90% power at a two-sided significance level of 0.05.

Table 2. Study treatments and interventions protocol

<table>
<thead>
<tr>
<th>Treatments and interventions</th>
<th>Early goal-directed sedation with DEX</th>
<th>Standard care sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia management</td>
<td>Boluses or infusions of opioids or other analgesics</td>
<td>Boluses or infusions of opioids or other analgesics</td>
</tr>
<tr>
<td>Primary sedative agents</td>
<td>DEX infusion at 1 µg/kg/hour (no loading dose). Titrate between 0 and 1 µg/kg/hour</td>
<td>Clinician choice of sedative agents by bolus or infusion. Likely, benzodiazepine, propofol or both</td>
</tr>
<tr>
<td>Sedation target range</td>
<td>RASS –2 to +1 (patient maintain eye contact &gt; 10 seconds) unless specified by treating clinician*</td>
<td>RASS –2 to +1 (patient maintain eye contact &gt; 10 seconds) unless specified by treating clinician*</td>
</tr>
</tbody>
</table>
| Additional sedation          | Propofol at lowest effective dose for:  
  • initial titration of DEX;  
  • optimise comfort when DEX at max tolerated dose is not enough; and  
  • immediate control of breakthrough agitation | Increasing infusion rate, additional boluses of sedative agents used above |
| Prohibited drugs             | Remifentanil and injectable clonidine. Benzodiazepines last resort, as below | Remifentanil and injectable clonidine. DEX last resort, as below |
| Patients requiring neuromuscular blockade after randomisation | Prevent awareness with propofol, continue DEX, may commence midazolam if required to ensure deep sedation | Prevent awareness at the discretion of the treating clinician |
| Breakthrough agitation       | Increases DEX to maximum tolerated dose at discretion of treating clinician to a maximum of 1.5 µg/kg/hour  
  Propofol bolus of infusion at the discretion of the treating clinician  
  Clinician choice of non-benzodiazepine antipsychotic agents, such as quetiapine (12.5–100 mg daily)14 and/or haloperidol 1–5 mg as required  
  For refractory agitation, benzodiazepine can be administered | Optimise current sedative agents  
  Clinician choice of antipsychotic agents, such as quetiapine (12.5–100 mg daily) and haloperidol 1–5 mg as required  
  For refractory agitation, DEX infusion can be administered |
| Per protocol consideration for benzodiazepines | Palliation, procedural amnesia, seizures, neuromuscular blockade and refractory agitation |  |

DEX = dexmedetomodine. RASS = Richmond Agitation Sedation Scale. * Analgesic management titrated to pain assessment. Sedative titration as per frequently measured RASS.
Statistical analyses

All statistical analyses will be conducted on an intention-to-treat basis, with patients analysed according to their assigned treatment arms, unless otherwise indicated (Figure 1). No imputation for missing data (<5%) will be performed for the primary analyses and the number of analysed observations will be reported. A sensitivity analysis using multiple imputation will be performed for missing data.
Met all inclusion criteria  
\( n = XXXX \)

Excluded  
\( n = XXXX \)

Reasons  
\( n = XXXX \)

Randomised  
\( n = XXXX \)

Assigned to receive early goal directed sedation  
\( n = XXXX \)

Assigned to receive standard care sedation  
\( n = XXXX \)

Non-septic  
\( n = XXXX \)

Septic  
\( n = XXXX \)

Day 90 vital status unknown  
- Consent withdrawn/refused  
\( n = XX \)

- Unable to be located  
\( n = XX \)

Analysed for primary outcome  
\( n = XXXX \)

Table 4. Study secondary and tertiary outcome

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>All-cause mortality 90-day after randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcomes</td>
<td>• Cognitive function (measured by IQCODE) and health-related quality of life (measured by EQ-5D-3L) at 180 days</td>
</tr>
<tr>
<td></td>
<td>• Residential institutional dependency at 180 days</td>
</tr>
<tr>
<td></td>
<td>• Mortality at 180 days after randomisation</td>
</tr>
<tr>
<td></td>
<td>• Ventilation-free days at 28 days after randomisation</td>
</tr>
<tr>
<td></td>
<td>• Coma and delirium-free days at 28 days after randomisation</td>
</tr>
<tr>
<td>Tertiary outcomes</td>
<td>• Mortality at ICU discharge</td>
</tr>
<tr>
<td></td>
<td>• Length of ICU stay</td>
</tr>
<tr>
<td></td>
<td>• Mortality at hospital discharge</td>
</tr>
<tr>
<td></td>
<td>• Length of hospital stay</td>
</tr>
<tr>
<td></td>
<td>• Duration of mechanical ventilation stratified by survival</td>
</tr>
<tr>
<td></td>
<td>• Incidence of delirium over entire length of ICU stay censored at Day 28</td>
</tr>
<tr>
<td></td>
<td>• Coma-free days at 28 days after randomisation</td>
</tr>
<tr>
<td></td>
<td>• Proportion of patients who:</td>
</tr>
<tr>
<td></td>
<td>▶ receive neuromuscular blockade after randomisation;</td>
</tr>
<tr>
<td></td>
<td>▶ require a tracheostomy;</td>
</tr>
<tr>
<td></td>
<td>▶ require re-intubation;</td>
</tr>
<tr>
<td></td>
<td>▶ require physical restraints; or</td>
</tr>
<tr>
<td></td>
<td>▶ had an unplanned extubation</td>
</tr>
<tr>
<td></td>
<td>• Proportion of patients who receive an active mobilisation episode during ICU stay or up to 28 days after randomisation</td>
</tr>
<tr>
<td></td>
<td>• Proportion of days were active mobilisations were delivered</td>
</tr>
<tr>
<td>Process-related outcomes</td>
<td>• Proportion of RASS measurements that are:</td>
</tr>
<tr>
<td></td>
<td>▶ within the target range of −2 to +1;</td>
</tr>
<tr>
<td></td>
<td>▶ −3 to −5 (deep sedation); and</td>
</tr>
<tr>
<td></td>
<td>▶ ≥ +2 (agitated state)</td>
</tr>
<tr>
<td></td>
<td>• Median daily dose of midazolam, propofol, DEX, fentanyl and morphine in patients who received these medications</td>
</tr>
<tr>
<td></td>
<td>• Duration of treatment with midazolam, propofol and DEX</td>
</tr>
</tbody>
</table>

DEX = dexmedetomidine. EQ-5D-3L = Euro Quality of Life 3 dimensions questionnaire. ICU = intensive care unit. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly. RASS = Richmond Agitation Sedation Scale.

Figure 1. CONSORT study flow diagram
> 5%. A two-tailed 5% level of significance will be used and \( P \) values will be adjusted for multiplicity as appropriate using the Bonferroni correction.

**Baseline characteristics**

A description of the baseline characteristics of the trial participants will be presented by treatment group. Discrete variables will be summarised as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table or in a footnote to the corresponding summary table. Continuous variables will be summarised by either means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate, according to the observed distribution of the variable.

**Primary outcome**

The effect of treatment allocation on all-cause mortality at 90 days after randomisation will be summarised using proportions in each treatment arm and assessed using binomial regression with an identity link function and adjusting for the binary sepsis stratification factor. This analysis will estimate the risk difference directly, together with a 95% CI and \( P \) value. In addition, an OR and 95% CI will be calculated by logistic regression to produce a ratio measure of effect adjusted for sepsis status. Sensitivity to missing data will be performed using multiple imputations, with imputation models based on prognostic baseline and post-baseline variables under a missing at random assumption. Sensitivity analyses of results to any differences between study sites and regions or variables exhibiting baseline imbalances will be performed using multivariable logistic regression with random effects for site.

**Secondary and tertiary outcomes**

**Secondary outcomes.** Binary secondary outcomes (Table 3) (ie, mortality and institutional dependency at 180 days) will be summarised using the observed proportions of the outcome in each treatment arm, and compared with logistic regression adjusting for sepsis status to produce ORs, 95% CIs and \( P \) values.

Cognitive function and quality of life at 180 days will be summarised with means and SDs, or medians and IQRs, as necessary according to the skewness of their distributions.

Ventilation-free days to Day 28 will be summarised using medians and IQRs in each treatment arm. Comparison of ventilation-free days across treatment arms will be performed using quantile regression adjusting for sepsis status, with the principal analysis being median regression (to estimate the difference in median number of days, with \( P \) value and 95% CI) and supplementary analyses using the 25th and 75th percentiles. In addition, the proportion of patients with a score of zero ventilation-free days will be tabulated by mortality status, which corresponds to patients continuously ventilated for at least 28 days or who died while still ventilated.

Delirium-free days at 28 days will be assessed using a composite measure of coma and delirium-free days, defined as the number of days up to Day 28 that each patient was free from both coma and delirium. Days in the ward after ICU discharge will be counted as delirium-free days.\(^{16}\)

Days without delirium or coma occurring within 28 days in deceased patients will be counted as delirium- and coma-free days respectively. In these patients, deaths within 28 days will not be scored as zero days when assessing delirium and coma-free days before death.

A secondary assessment of delirium will take into account that delirium cannot be assessed when a patient’s sedation level is below a RASS of –2 (coma), and that ICU discharge and death are competing events for terminating the observation period of follow-up. This will be performed using a joint modelling approach in which both daily delirium risk and the risk of death or ICU discharge are modelled simultaneously, as described by Colantuoni and colleagues.\(^{17}\) The effect of EGDS is included in the model for delirium, regarded as a recurrent event in this time-to-event model, and which excludes days in a coma from the period a patient is at risk of delirium. This model is then linked with a time-to-event model for ICU discharge or death by the incorporation of daily delirium as a time-dependent covariate. In this manner, the effects of EGDS on delirium and the effect of delirium on daily death or discharge risk are modelled together. The interpretation of the EGDS term in the delirium model is of fundamental interest — it is the comparison between EGDS and usual care on the daily risk of delirium, taking death and ICU discharge into account.

**Tertiary outcomes.** The primary assessment of RASS measurements will categorise each measurement for each patient as:

a. within the target range of –2 to +1;

b. –3 or lower (deep sedation); or

c. +2 or higher (agitated state).

These measurements will be aggregated over patients within each treatment arm in each day to produce proportions in each category, and these proportions will be graphed over time for each treatment arm. Comparison of the proportions of measurements in ranges (a)–(c) between treatment arms, over the first 48 hours and while mechanically ventilated, will be made using multinomial logistic regression of the individual RASS measurements, with robust standard errors clustered at individual patient level to account for correlation between repeated RASS assessments within and between days. These analyses
compare the proportion of RASS measurements within each range for each patient within each day, weighted by the number of RASS measurements made in total over the day. Sensitivity of the results of this analysis to missing RASS assessments will be performed using multiple imputation to “fill in” missing RASS measurements using imputation models that incorporate pre- and post-randomisation variables — together with treatment arm — that are considered predictive of the missing RASS measurements and as to whether RASS measurements were missing or not.

A secondary analysis of the RASS measurements will use the recently developed sedation index (SI), which is a sedation measure on a continuous scale taking into account the time dimension and the level of sedation delivered. The SI is defined as the weighted average sedation score over the time period of interest, the first 48 hours and while mechanically ventilated, with the weight for each subject being the proportion of the total number of RASS measurements indicating sedation. The average SI scores will be compared between EGDS and usual care arms using descriptive statistics, and will be modelled using linear regression with EGDS and sepsis status and region as covariates, and with a robust sandwich error to allow for non-constant variances between arms.

Analyses of length of stay in ICU and in hospital will employ methodology that takes the competing risk of death (in ICU or hospital, respectively) into account. Graphical displays of length of stay in ICU and hospital in each treatment arm will be presented using cumulative incidence functions (CIFs), which estimate the incidence of an event (discharge) each day while taking the competing risk of death into account. For example, in such graphs, the treatment arm with a steeper slope indicates a faster rate of discharge. Comparison of discharge (incidence) rates between treatment arms will be performed using subdistribution hazard regression models, a variant of conventional Cox proportional hazard regression, in which regression coefficients are interpreted as the relative discharge probability on a given day between the two treatment arms in patients who have not yet been discharged, together with a $P$ value and 95% CI. These models will also include a term for sepsis status and site and the assumption of proportionality of hazards will be checked by interaction terms between treatment arm and time. The SAS PHREG procedure (with event-code option) will be used to fit these models.

Process-related outcomes, in each treatment arm, will be summarised with means and SDs, or medians and IQRs, as necessary, according to the skewness of their distributions. Correspondingly, either linear or quantile (median) regression will be performed to compare treatment arms, adjusting for sepsis status.

Discharge destination proportions will be tabulated for each treatment arm, with categories designated as home, rehabilitation facility, nursing home and other acute hospital. These proportions will be modelled with multinomial logistic regression to compare treatment arms with adjustment for sepsis status.

Subgroup analyses

Potential heterogeneity of the risk difference of the primary endpoint across specified subgroups will be assessed using binomial identity regression, with treatment group, sepsis status and the subgroup identifier incorporated as main effects together with a multiplicative interaction term between treatment and the subgroup identifier. Likewise, heterogeneity of treatment effects for the secondary endpoints will employ analogous terms in the respective regression models listed above. All such subgroup analyses will be exploratory, and the potentially reduced power of such tests to find evidence of significant interactions is acknowledged. These results will be reported as a forest plot. The specific subgroups that will be considered are:

- sepsis status;
- age below and at or above the median age;
- Acute Physiology and Chronic Health Evaluation (APACHE) II score below and at or above the median APACHE II score;
- $P_{a}/F_{io2}$ ratio below and at or above the median value;
- surgical and medical diagnosis (using the APACHE II definition); and
- region — Australia and New Zealand, Europe, and Malaysia and Saudi Arabia (combined).

Consenting and ethical compliance

Due to the nature of the trial and the narrow randomisation window, prior informed consent is not usually possible. Therefore, where allowed under regional legislation, and when approved by the appropriate ethics committee, participants are enrolled into the trial without consent and the participant or their legal surrogate is asked for consent to continue as soon as reasonably practicable. Two situations may result in cessation of trial treatment:

- the patient or legal surrogate may decline consent to continue trial treatments; or
- the patient or legal surrogate may withdraw consent to continue in the trial.
In both cases, trial specific treatments will cease and the patient will continue sedation therapy as prescribed by the treating clinician. When this situation occurs, consent to data collection is sought, and if this is declined, the patient's data are removed from the website and not analysed, apart from data related to randomisation and consent. For trial participants who decline consent only to ongoing study treatments, but allow use of data, these data will be included and analysed on an intention-to-treat basis.

Data safety monitoring board
An independent data safety monitoring board (DSMB) oversees and reviews all serious adverse events and receives study data at predetermined intervals or as necessary. A detailed DSMB Charter was approved by the DSMB and the study management, with explicit stopping, reporting and communication rules. The DSMB is chaired by Derek Angus (University of Pittsburgh, United States) with Joyce Chang (biostatistician), Jeremy Kahn and Damon Scales as independent members.

A single, planned, formal interim analysis was performed once 90-day outcome data from the first 2000 participants enrolled were available. The DSMB recommended continuation of enrolment.

Conclusion
SPICE III is an ongoing randomised multinational controlled trial to recruit a total of 4000 patients comparing a process of EGDS with standard care in critically ill patients who are expected to require mechanical ventilation for more than 24 hours. Once completed, this trial will inform sedation practice in critically ill patients who are ventilated.

Competing interests
The SPICE program and this trial is investigator-initiated. The study is primarily funded by project grants from the Australian National Health and Medical Research Council and the New Zealand Health Research Council. The study drug dexmedetomidine is provided to some study sites free of charge, as in-kind support to the trial, by Pfizer (formerly Hospira) and Orion Pharma. The study concept, design, conduct, data collection, monitoring, data analysis and any publications are totally independent from funding agencies; in particular, Pfizer and Orion Pharma have no involvement in any aspects of the study conduct.

The authors approve the final manuscript and declare no conflict of interest in relation to this manuscript. Yahya Shehabi received unrestricted research grants from Monash University and participated in educational symposia funded by Pfizer and Orion Pharma, he reported travel expenses and speakers honorarium reimbursed to his employer. Jukka Takala, through the Department of Intensive Care Medicine at Bern University Hospital, and the University of Bern, has or has had research and development and consulting contracts with Orion Corporation, Abbott Nutrition International, B Braun Medical, CSEM, Edwards Lifesciences Services, Kenta Biotech, Maquet Critical Care, Omnicare Clinical Research and Nestlé. He has received unrestricted educational grants from Fresenius Kabi, GSK, MSD, Lilly, Baxter, Astellas, AstraZeneca, B Braun Medical, CSL Behring, Maquet, Novartis, Coviden, Nycomed, Pierre Fabre Pharma (Roba Pharma), Pfizer and Orion Pharma. No personal financial gain resulted to Jukka Takala from these contracts and educational grants. Suhaini Kadiman has a consulting agreement with the Edwards Lifesciences (Malaysia) and received unrestricted grants from the National Heart Institute Foundation of Malaysia. Michael Reade was the chief investigator of a trial involving dexmedetomidine that was in part funded by an unrestricted grant from Pfizer, and has contributed to educational symposia funded by Pfizer and CSL Behring. Matthew Wise has received travel and accommodation to an education meeting sponsored by Orion, an advisory board fee from Baxter Healthcare and a lecture fee from an educational meeting sponsored by Jazz Pharmaceuticals. Yaseen Arabi, Rinaldo Bellomo, Andrew Forbes, Colin McArthur, Steve Webb, Frances Bass and Belinda Howe declare no conflict of interest.

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References