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ORIGINAL

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Registration and design alterations of clinical trials in critical care: a cross-sectional observational study

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Take-home message: This study found that one-third of critical care medicine (CCM) trials published after July 2005 have not been registered; of those that were registered, registration occurred during—or after completion of—patient enrolment in two-thirds of studies. In well over half of trials that were registered, the primary outcome or sample size was potentially altered between initial registration and final publication. These findings suggest serious problems with reporting and conducting randomized controlled trials in CCM.

A related editorial can be found at doi: 10.1007/s00134-014-3265-0.

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Abstract *Purpose:* In 2005 the International Committee of Medical Journal Editors issued a requirement that all randomized controlled trials (RCTs) be registered primarily to prevent selective reporting (publication bias). However, registries allow for alterations in study protocol. Changes occurring before (or after) study completion could invalidate the original study intent, leading to publication of misleading conclusions. In RCTs involving critically ill patients, these concerns may be particularly acute because mortality is high and conditions investigated are usually syndromes rather than specific diseases. This study was conducted to estimate the registration rate of RCTs in critical care; and, among registered RCTs, to determine timing of registration and whether sample size or primary outcome were altered. *Methods:* We searched the MEDLINE database for RCTs that began after or continued through July 2005. We determined whether each trial had been registered and, for registered trials, compared registry data to data in the published manuscript. *Results:* Approximately two-thirds (66 %) of trials were registered. Of these, 66 % of registrations occurred after enrolment had commenced. Overall, 6 % (5/90) of trials appropriately registered a sample size which was unchanged from the interval between registration and publication, and only 12 % (11/90) reported primary outcomes that were both appropriately registered and unchanged. *Conclusions:* Non-registration, or registration after trial initiation, are common in RCTs of critically ill patients. Among registered trials important protocol changes are often made between trial commencement and publication. This study identifies and quantifies the extent of this serious—but correctable—problem for RCTs in critically ill patients.

Keywords Registration · Critical care · Registry · Sample size · Primary outcome

Introduction

The randomized controlled trial (RCT) is preferred for testing cause–effect relationships between treatments and outcomes [1] but its validity depends upon several important elements. Two important components of an RCT are the primary outcome—the principle issue being tested—and the anticipated sample size. A larger sample size is required in studies where the between-group difference in primary outcome (i.e. effect size) is small, or where its variance is large; thus these two key elements are interrelated [2].

Changing a primary endpoint after enrolment has begun changes the principle purpose of the research; it also changes the original assumptions that were used to calculate the required sample size. Similarly, changing the sample size while the trial is underway suggests an inability to enrol adequate numbers of patients, or that the anticipated effect size was incorrect. Nonetheless, while changing the primary endpoint or sample size after enrolment has commenced can undermine the validity of a study, transparent reporting facilitates detection and understanding of such changes.

Recognizing such concerns, the National Institutes of Health (NIH) and other agencies created databases for trial pre-registration. Supporting this initiative, the International Committee of Medical Journal Editors (ICMJE) agreed that RCTs would not be considered for publication unless they had been registered with a minimum dataset [3, 4]. Using such registration databases, journal reviewers and readers can determine the originally recorded intentions of the study and whether (and when) such plans had been changed. In addition, pre-registration enables better identification of publication bias, protecting against the non-publication of 'negative' studies [5].

Understanding the timing of trial registration may provide important insight into the significance of alterations in the study plan. Changes that occurred between trial completion and publication may have been prompted by the final results, whereas changes occurring during patient enrolment may have been triggered by the accumulating study data. In contrast, the combination of registration before commencement of patient enrolment coupled with no subsequent design changes (or restriction to well-justified changes) ensures that neither emerging nor completed study data would have influenced the study design as reported in the final manuscript. While the original requirement was for registration before commencement of patient enrolment [3, 4], 'appropriate' registration has more recently been characterized as that occurring before completion of the trial [6].

Changes in study design may have particular impact on RCTs of critically ill patients, where the presence of multiple therapies and co-morbidities is common [7–9]. In addition, because of the high mortality, morbidity and economic cost associated with critical illness, it is especially important to design studies with sufficient power to determine with certainty whether therapies investigated in trials are truly effective—or not [10]. Altering the intended outcome during trial conduct can introduce similar barriers to understanding the effectiveness of a tested intervention. These concerns are heightened in the critically ill because a large majority (over 90 %) of multicenter RCTs in critical care medicine (CCM) that specify mortality as a primary endpoint reported that the tested intervention was non-beneficial [11].

Because pre-registration can facilitate insight into the validity of an RCT, and because this may be especially important in the critically ill, we investigated trial registration and post-registration trial alterations in published RCTs of treatments in ICU patients.

Methods

Search and selection criteria

We searched the MEDLINE database (August 2011) using OVID Medline to identify RCTs that were published in the discipline of CCM using the following MeSH terms: "Critical Care", "Critical Illness", "Intensive Care Units", "Respiratory Distress Syndrome, Adult", "Sepsis", "Multiple Organ Failure", and "Respiration, Artificial". We limited our search to include only trials conducted in humans and published in English-language journals ("English language" and "humans") and used the validated search term "randomized controlled trials" (pt). We also chose to limit our search to studies published after 2005 ("2005–August 2011") because most major medical journals required trial registration by this date.

Two reviewers (VA, BK) independently screened studies for inclusion according to the following criteria: trials involving interventions in intensive care units, burn units, or pulmonary care units. Exclusion criteria included completion of enrolment before July 2005; focus on perinatal or neonatal issues, pharmacokinetics, follow-up clinics, caregiver knowledge or validation of scoring systems; secondary analyses of a prior study; retracted manuscripts; studies of pre- or intraoperative interventions; and studies in healthy volunteers or in sleep laboratories.

We searched for trials published since 1 July 2005 because the 2004 ICMJE statement stipulated that trials commencing after this date must be registered at or before the onset of enrolment. However, the ICMJE recognized that trials already commenced prior to this date might not yet have been registered, and required that such ongoing or completed trials be registered before 13 September 2005 to be considered for publication.

The registry identification number was recorded from the manuscript. For published trials that did not include their registry data, a search using the name of the first and

last author (and the corresponding author, where this was neither the first nor last author) was conducted in the three most commonly used registration databases: ClinicalTrials.gov (NCT), controlled-trials.com (ISRCTN), and anzctr.org.au (ACTRN). If registration information was not identified, an email was sent to the corresponding author to enquire about registration status.

Manuscript review

Two reviewers independently abstracted information from the published manuscript of each registered trial. The enrolment start and end dates were recorded, if reported. If no enrolment date was reported, enrolment commencement and cessation dates from the registry were used, where available. The primary outcome of the study was recorded; if none was specified, the outcome variable that was used to determine sample size was assumed to be the primary outcome. If the reviewers were still unable to determine a primary outcome, the primary outcome was recorded as 'unclear'. If more than one primary outcome (or primary efficacy or safety endpoints) were reported, all were recorded. The number of enrolled patients that were included in the final analysis was also recorded.

Registry review

Two reviewers abstracted the following information from the online registry: registration date, primary outcome, anticipated sample size. The date on which the study was registered in the database was recorded, as was the proposed primary outcome(s), as well as any dates that these were entered or altered. If a primary outcome was not recorded at the time of registration, but was subsequently appended, they were reported as 'added'. The anticipated enrolment size was recorded as present or not.

Evaluation measures

The enrolment start and end dates (from the published paper) were compared to the trial registration date (from the registry). Studies in which enrolment commenced after 1 July 2005 (the date stipulated by the ICMJE statement) were examined for registration date and these dates were recorded as 'registered before patient enrolment commenced', 'registered during patient enrolment', and 'registered after patient enrolment was completed'.

For trials that commenced before, but continued after 1 July 2005, registration was recorded as 'studies registered on or before September 2005' or 'studies registered after September 2005'.

Primary outcomes and sample size

Changes in the primary outcome(s) between initial registration and publication in the manuscript primary outcome(s) were recorded; all detected changes were confirmed by three reviewers (BK, DS, CP) independently and then in conference. Consensus was used to resolve any disagreements. We a priori defined as important a difference in sample size of 10 % or more between that originally registered and that reported in the published manuscript.

ICMJE status

For each journal from which a trial was included in the analysis, their listing status with ICMJE was recorded. The source of this information was http://www.icmje.org/journals.html (journals following ICMJE recommendations).

Results

Our search identified 2,308 published studies and 197 trials met our eligibility criteria (Fig. 1). Overall, 133 (of 197; 68 %) trials were registered in a trials registry; 105 reported the registry number in the manuscript and 28 were found by registry searches. Most studies were registered with ClinicalTrials.gov ($n = 103$) or Controlled-Trials.com ($n = 25$), and 5 studies were registered with the Australian New Zealand Clinical Trials Registry. One study reported incorrect registration information but was nonetheless included in our analysis. For two studies in which enrolment completion was not recorded in the publication, the completion date from the registry was used. Five studies had incomplete enrolment date information in both publication and registry, and were excluded from further analysis. The included studies were divided into those starting enrolment after July 2005 ($n = 90$; Fig. 1) vs. those in which enrolment commenced before July 2005 ($n = 107$; Fig. 1).

Enrolment commenced after July 2005

Registration and timing of registration ("Appendix 2")

Two-thirds (59/90; 66 %) of trials commencing after July 2005 were registered (Fig. 1). Of the 59 registered trials, 20 (34 %) were registered before patient enrolment began, 23 (39 %) were registered during the enrolment phase of the trial, and 16 (27 %) were registered after enrolment was completed (Fig. 1). Approximately one-third (31/90; 34 %) did not have identifiable registration information; in these cases the corresponding author was

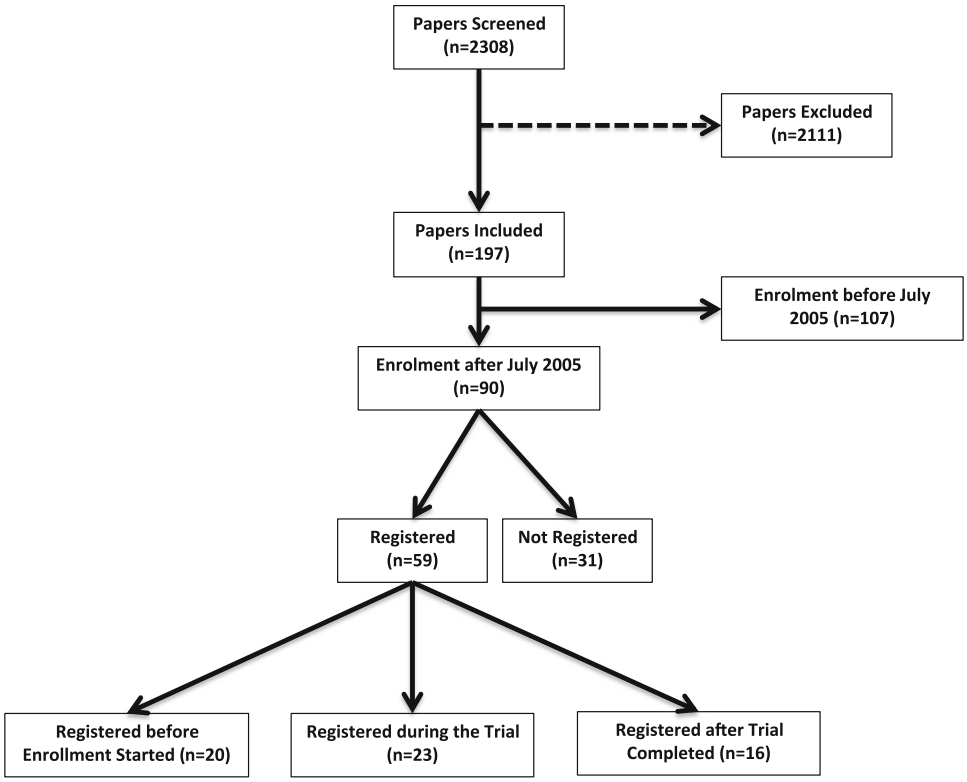

Fig. 1 Study flow chart: enrolment after July 2005 = trials where the entire enrolment occurred after July 2005; enrolment before July 2005 = trials where enrolment began before July 2005 but continued after July 2005

contacted, nine of whom confirmed non-registration. No additional registration information was available.

Sample size ("Appendix 3")

Of the 90 critical care trials included in the study, 5 (6 %) articles were both appropriately registered (registered prior to study enrolment), and had unchanged sample size from registration to publication (Fig. 2). In total 55 % (11/20) of pre-registered trials changed sample size by at least 10 %. Of trials registered during enrolment, 11/23 (48 %) changed the sample by at least 10 %; of these 82 % (9/11) were revised to a lower value. In a further 19 % (11/59) of registered trials the original sample size recorded in the registry was unclear.

Primary outcome ("Appendix 4")

Eleven of 90 (12 %) trials were appropriately registered and unchanged (Fig. 3). In 25 % (15/59) of registered trials a change was made in published primary outcome from that recorded in the registry. In 56 % (33/59) of registered trials a change in primary outcome was unclear either because of the lack of clearly identifiable primary outcome or because registration occurred after the trial enrolment began. Changes to a primary outcome often involved the reporting of mortality (3/7 RCTs registered pre-enrolment and 3/6 registered mid-enrolment) ("Appendix 7").

Enrolment commenced before July 2005

Registration and timing of registration

For 107 studies in which enrolment commenced prior to July 2005 and continued through 13 September 2005, 74 (69 %) were registered; of these almost one-third (35 %, 26/74) were registered after enrolment was complete.

ICMJE status

Comparisons were made between papers published in journals listed as following ICMJE recommendations ('Listed') vs. papers published in journals that were not listed as following ICMJE recommendations ('Non-listed'). Registration was confirmed in 83 % of papers published in 'Listed' journals vs. 57 % published in 'Non-listed' journals (Table 1; $p = 0.019$, OR 3.57, 95 % CI 1.09–12.35). Sample size was changed (by $\geq$10 %) in 30 % of papers published in 'Listed' journals vs. 64 % of papers published in 'Non-listed' journals (Table 2; $p = 0.02$, OR 0.24, 95 % CI 0.06–0.95). Finally, primary outcome was changed in 30 % of papers published in 'Listed' journals vs. 26 % of papers published in 'Non-listed' journals (Table 3. $p = 0.73$).

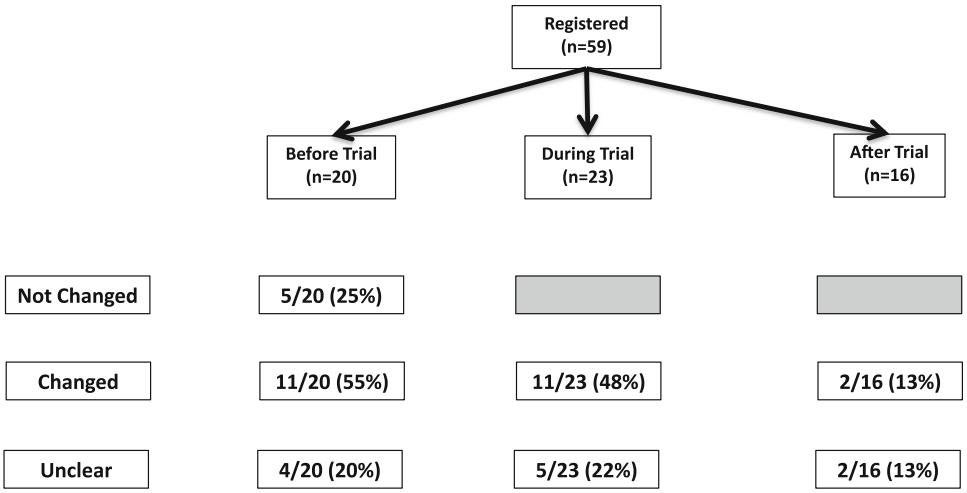

Fig. 2 Sample size in trials where all enrolment occurred after July 2005: before trial = registration occurring before trial enrolment or "pre-registration"; during trial = registration occurring while trial enrolment was ongoing; after trial = registration occurring after trial enrolment was completed or "post-registration"; not changed = trials where sample size was clearly not altered from registration to publication; changed = trials where sample size was definitely changed from registration to publication; unclear = trials where alteration of sample size was unclear

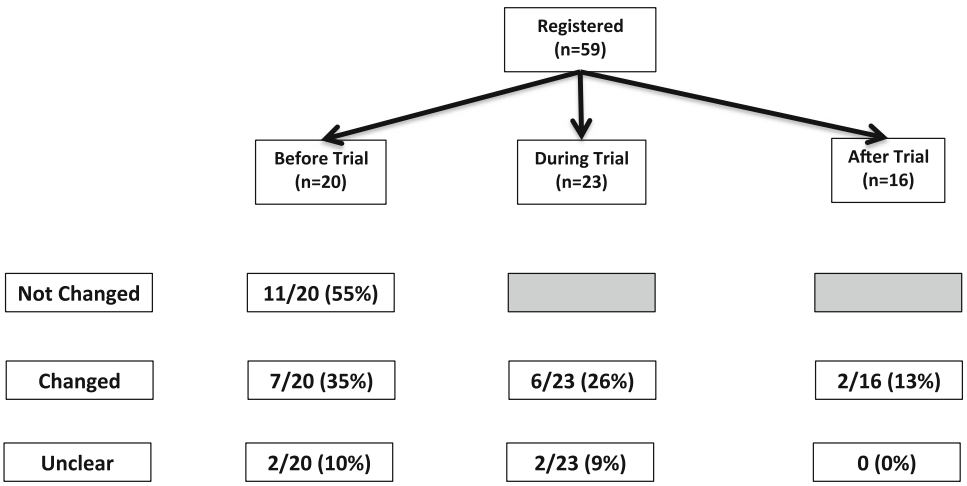

Fig. 3 Primary outcome in trials where all enrolment occurred after July 2005: before trial = registration occurring before trial enrolment or "pre-registration"; during trial = registration occurring while trial enrolment was ongoing; after trial = registration occurring after trial enrolment was completed or "post-registration". Not changed = trials where primary outcome was clearly not altered from registration to publication; changed = trials where primary outcome was definitely changed from registration to publication; unclear = trials where alteration of primary outcome was unclear

Table 1 Registration and ICMJE journal listing

	Papers published in ICMJE listed journal	Papers published in non-ICMJE listed journal
Registered (%)	83 % (24/29)	57 % (35/61)
Non-registered (%)	17 % (5/29)	43 % (26/61)
Total	29	61

11 excluded due to unclear results

Discussion

We systematically evaluated published RCTs in critical care commencing enrolment after July 2005 and were unable to find an associated registration in over one-third. Thus, as in other areas of medicine [6, 12–14], clinical trials conducted in critically ill patients frequently do not conform to the recommendations of the ICMJE statement [3, 4]. Of trials in critically ill that were registered (at any

Table 2 Changes in sample size and ICMJE journal listing

	Papers published in ICMJE listed journal	Papers published in non-ICMJE listed journal
Sample size changed (%)	30 % (6/20)	64 % (18/28)
Sample size not changed (%)	70 % (14/20)	36 % (10/28)

11 (of the 59 registered studies) excluded from this table due to unclear results

Table 3 Changes in primary outcome and ICMJE journal listing

	Papers published in ICMJE listed journal	Papers published in non-ICMJE listed journal
Primary outcome changed (%)	30 % (6/20)	26 % (9/35)
Primary outcome not changed (%)	70 % (14/20)	74 % (26/35)

4 (of the 59 registered studies) excluded from this table due to unclear results

time), registration occurred either during or after completion of patient enrolment in two-thirds of studies. In addition, among trials with significant changes in study design (i.e. sample size or primary outcome) between initial registration and eventual publication, the majority of these changes occurred during or after patient recruitment. Finally, our results likely underestimate the extent of this problem because protocol changes in trials that were not registered until after study completion cannot be detected; in addition while ClinicalTrials.gov allows tracking of protocol changes, other registries are not as easily tracked.

The ICMJE statement on trial registration was intended to minimize publication bias and increase transparency in reporting of trials. Such registration helps protect against selective reporting (and duplication of results) because investigators publicly declare the methodology and study purpose [3, 4], and do not alter these except for sound reasons that should be articulated. Registration helps confirm the study's internal validity where primary outcomes and sample size remain as determined at the design phase. In contrast, internal validity is undermined if the outcomes or target sample size is shaped by evolving (or final) results. Thus, our finding that less than a fifth of all trials registered were done so before patient enrolment began and clearly did not change the primary outcome between registration and publication suggests that published manuscripts might not accurately represent the original study intent or design.

We found that the anticipated sample size frequently differed between initial registration and manuscript publication; when such discrepancies occurred, the published sample size was usually lower than that initially recorded. Reducing sample size during the conduct of a study may render the study underpowered to detect a clinically important difference between groups [10, 15]. Conversely, studies that report significant between-group differences should be viewed with skepticism where the sample size has been markedly reduced during the course of the study [16]; in these cases, the effect size (i.e. the magnitude of the apparent treatment benefit) is frequently overestimated, as has been described in cases of premature trial termination for apparent benefit [17].

We focused on trials in the critically ill because such studies may be particularly susceptible to the problems created by inadequate trial registration. For example, important heterogeneity exists in many aspects of these patients. Illness definitions—and thus criteria for trial entry—in such patients are usually syndromes (e.g. sepsis, acute respiratory distress syndrome) rather than specific disease entities; as well, management is often multifaceted and co-morbidities are common. Thus, trials in these patients involve much 'study noise', making imperative the standardization and consistency of trial management. These factors may explain, in part, why the overwhelming majority (over 90 %) of multicenter RCTs with mortality as a primary endpoint in this population report that the tested interventions were not beneficial [11].

Studies testing mortality as the primary endpoint may be the most important to patients. Because critically ill patients have very high levels of mortality [18], morbidity [19–23] and economic cost [24], design changes that may contribute to incorrect or misleading reports assume a high priority. In addition to such concerns, there are ethical implications: altering the design of a study after consent has been obtained could compromise the nature of the consent [10], and may be especially important in CCM where consent is frequently through a third-party [25]. When changes to primary outcome were recorded, these often involved the reporting of mortality (3/7 RCTs registered pre-enrolment with subsequent changes and 3/6 registered mid-enrolment). We believe this is a conservative number, as several studies had multiple primary endpoints making it unclear if 'the' primary endpoint was changed.

Previous reports have raised concerns about the discrepancies between registered and published trial methodologies. Mathieu and colleagues evaluating trials from three different subspecialties (cardiology, rheumatology, and gastroenterology) reported that over 50 % of trials were not 'adequately' registered [6], and among these studies, the primary outcome was altered in one-third of trials, almost always (over 80 %) conferring 'statistical advantage' towards a positive trial result. However, this may be an underestimate of the problem, as in that report [6] registration was considered to be 'adequate' provided it occurred before study completion, thereby missing—in those studies—any design changes that may have been made during patient enrolment.

Other issues can undermine trial registration. For example, a study of trial registration in Canada reported

non-compliance with identification of trial leadership and contact information, two (of the 20) important items identified as necessary by the ICMJE [26].

Lack of adherence to the principles outlined in the 2005 ICMJE statement [3, 4] may occur for several reasons, including lack of understanding or acceptance by researchers, inadequate review of registration data by manuscript reviewers, and insufficient oversight from editorial boards. However, in some cases lack of adherence may reflect a desire to change sample size or primary outcome in order to enhance the likelihood of earlier publication, or publication in a higher-impact journal. Our data suggest that attention to the timing of registration, as well as changes in key elements such as sample size and primary outcome, could enhance registry benefit in studies of the critically ill.

There are important limitations to our findings. First, the evaluation focused on trials in CCM, and thus may not reflect the prevalence of inadequate registration in other disciplines. In fact, review of trial registration in other subspecialties (i.e. cardiology, rheumatology, and gastroenterology) has revealed comparable rates registration, although sample size alterations during the study were not sought [6].

The study was limited to a relatively small time span (i.e. 6 years since the publication of the ICMJE statement) [3, 4]. This may be important because trials that have commenced since 2005 might not yet be completed or published, and therefore rates of pre-commencement trial registration might now be greater than reported in this study. However, while the detection of discrepancies between registered and published trial information is facilitated by insistence on pre-commence registration, such changes can still occur. Our analysis of ICMJE status is limited since there may be journals not listed with the ICMJE who follow the guidelines, and conversely there may be some journals listed with the ICMJE who do not follow all of the recommendations. We acknowledge that our search strategy may have missed a small number of trials that may be relevant to our study, but the intent of our analysis was not to be exhaustive; rather, it was to identify whether or not there were issues with registration practices in critical care literature.

While our study describes the frequency of deviation from initially specified sample size and primary outcome, we are unable to determine the reasons behind these changes and cannot exclude the possibility that some alterations—although not explained in the respective manuscripts—were based on sound reasoning. Furthermore, the ability to easily track changes in a trials registry is key to transparency. The ability to track changes is not readily available across all registries, and not in an intuitive fashion. An additional complication is that the terminology permitted (by registries and journals) sometimes results in a lack of clarity relating to key elements (e.g. sample size, primary outcome).

In conclusion, these data suggest that registration of clinical trials in the critically ill is frequently omitted, and among trials that are registered, the timing of registration and the presence of study alterations are usually not apparent in the published paper. There seems little justification for delaying trial registration until after patient enrolment has begun; indeed protocol changes that result in publication of potentially invalid data may be a greater problem than selective reporting, the prevention of which was the main intent of these registries. Changes in trial design occurring after a study has commenced (and certainly after it is complete) should be documented and justified for peer-reviewers and for readers.

Conflicts of interest None.

Appendix 1: Registration vs non-registration with ICMJE listing status

Registered

	ICMJE
Anderson (2008) Lancet Neurology	Y
Arcangeli (2010) Thrombosis Research	N
Azoulay (2010) American Journal of Respiratory & Critical Care Medicine	Y
Barbosa (2010) Critical Care	N
Barraud (2010) Intensive Care Medicine	N
Beale (2008) Critical Care Medicine	N
Blaha (2009) Diabetes Care	Y
Boerma (2010) Critical Care Medicine	N
Bouadma (2010) Lancet	Y
Burtin (2009) Critical Care Medicine	N
Cader (2010) Journal of Physiotherapy	Y
Cantaluppi (2008) Intensive Care Medicine	N
Cheung (2010) Critical Care & Resuscitation	N
Chung (2010) Critical Care Medicine	N
Cohen (2009) Critical Care (London, England)	N
Constantin (2010) Critical Care (London, England)	N
Dongelmans (2009) Anesthesia & Analgesia	Y
Dubin (2010) Journal of Critical Care	N
Endre (2010) Kidney International	N
Figueroa-Casas (2010) Respiratory Care	N
Frohmader (2010) American Journal of Critical Care	N
Gerovasili (2009) Critical Care (London, England)	N
Gupta (2010) Respiratory Care	N
Hernandez (2010) Chest	Y
Hochreiter (2009) Critical Care (London, England)	N
Holzinger (2010) Diabetes Care	Y
Holzinger (2011) Critical Care Medicine	N
Investigators (2009) New England Journal of Medicine	Y
Investigators (2010) JAMA	Y
Jabre (2009) Lancet	Y
Jansen (2010) American Journal of Respiratory & Critical Care Medicine	Y
Jones (2010) JAMA	Y
Loisa (2007) Critical Care (London, England)	N
Meisel (2009) American Journal of Respiratory & Critical Care Medicine	Y

Appendix 1 continued

Mentzelopoulos (2009) Archives of Internal Medicine	Y
Moraes (2009) Jornal de Pediatria	Y
Morelli (2008) Critical Care (London, England)	N
Morelli (2009) Critical Care (London, England)	N
Naidech (2010) Neurocritical Care	N
Nobre (2008) American Journal of Respiratory & Critical Care Medicine	Y
Olson (2009) Neurocritical Care	N
Ouellet (2009) The American Journal of Surgery	Y
Papazian (2010) New England Journal of Medicine	Y
Perez-Barcena (2008) Nutrition	N
Pichamuthu (2010) Clinical Toxicology	Y
Pieracci (2009) Surgical Infections	N
Reade (2009) Critical Care (London, England)	N
Richir (2009) Pharmalogical Research	N
Robinson (2010) Critical Care (London, England)	N
Roquilly (2011) JAMA	Y
Rose (2008) Intensive Care Medicine	N
Routsi (2010) Critical Care (London, England)	N
Shariatpanahi (2010) Journal of Critical Care	N
Staudinger (2010) Critical Care Medicine	N
Strom (2010) Lancet	Y
Timsit (2009) JAMA	Y
van Eijk (2010) Lancet	Y
Walz (2010) Critical Care Medicine	N
Xirouchaki (2008) Intensive Care Medicine	N

Unable to identify registration

	ICMJE
Acosta-Escribano (2010) Intensive Care Medicine	N
Baldasso (2009) Intensive Care Medicine	N
Bellissimo-Rodrigues (2009) Infection Control & Hospital Epidemiology	N
Bodur (2008) Anaesthesia & Intensive Care	Y
Boussekey (2008) Intensive Care Medicine	N
Cabov (2010) Wiener Klinische Wochenschrift	N
Chanques (2009) Intensive Care Medicine	N
Chen (2009) Journal of the Chinese Medical Association: JCMA	N
Chittawatanarat (2010) Asia Pacific Journal of Clinical Nutrition	N
Cianchi (2010) British Journal of Anaesthesia	Y
Clec'h (2008) Intensive Care Medicine	N
Devlin (2010) Critical Care Medicine	N
Dijkstra (2010) Journal of Clinical Nursing	N
Fields (2008) Journal of Neuroscience Nursing	N
Guo (2007) Journal of Huazhong University of Science and Technology Medical Sciences	N
Henricson (2008) Complementary Therapies in Clinical Practice	N
Johannigman (2009) Journal of Trauma-Injury Infection & Critical Care	N
Knowles (2009) Critical Care Medicine	N
Lucangelo (2008) Critical Care Medicine	N
Mahdy (2009) Middle East Journal of Anesthesiology	N
Mao (2010) Chinese Medical Journal	Y
Montejo (2010) Intensive Care Medicine	N
Morelli (2008) British Journal of Anaesthesia	Y
Peng (2010) Cytokine	N
Peng (2010) International Journal of Artificial Organs	N
Rowen (2007) Coronary Artery Disease	Y

Appendix 1 continued

Samransamruajkit (2010) Journal of Critical Care	N
Schroeder (2009) Langenbecks Archives of Surgery	N
Seder (2010) Critical Care Medicine	N
Weinberg (2008) Journal of Trauma-Injury Infection & Critical Care	N
Wiryana (2009) Acta Medica Indonesiana	N

Appendix 2: Timing of registration

Registered prior to trial enrolment

Anderson (2008) Lancet Neurology
Barraud (2010) Intensive Care Medicine
Beale (2008) Critical Care Medicine
Bouadma (2010) Lancet
Cheung (2010) Critical Care & Resuscitation
Endre (2010) Kidney International
Figueroa-Casas (2010) Respiratory Care
Investigators (2009) New England Journal of Medicine
Jabre (2009) Lancet
Jansen (2010) American Journal of Respiratory & Critical Care Medicine
Jones (2010) JAMA
Meisel (2009) American Journal of Respiratory & Critical Care Medicine
Naidech (2010) Neurocritical Care
Nobre (2008) American Journal of Respiratory & Critical Care Medicine
Papazian (2010) New England Journal of Medicine
Roquilly (2011) JAMA
Rose (2008) Intensive Care Medicine
Strom (2010) Lancet
Timsit (2009) JAMA
van Eijk (2010) Lancet

Registered during trial enrolment

Azoulay (2010) American Journal of Respiratory & Critical Care Medicine
Boerma (2010) Critical Care Medicine
Chung (2010) Critical Care Medicine
Dongelmans (2009) Anesthesia & Analgesia
Dubin (2010) Journal of Critical Care
Frohmader (2010) American Journal of Critical Care
Gerovasili (2009) Critical Care (London, England)
Gupta (2010) Respiratory Care
Hernandez (2010) Chest
Holzinger (2010) Diabetes Care
Holzinger (2011) Critical Care Medicine
Investigators (2010) JAMA
Mentzelopoulos (2009) Archives of Internal Medicine
Morelli (2008) Critical Care (London, England)
Morelli (2009) Critical Care (London, England)
Ouellet (2009) The American Journal of Surgery
Pieracci (2009) Surgical Infections
Reade (2009) Critical Care (London, England)

Appendix 2 continued

Richir (2009) Pharmalogical Research
Routsi (2010) Critical Care (London, England)
Staudinger (2010) Critical Care Medicine
Walz (2010) Critical Care Medicine
Xirouchaki (2008) Intensive Care Medicine

Registered after trial enrolment

Arcangeli (2010) Thrombosis Research
Barbosa (2010) Critical Care
Blaha (2009) Diabetes Care
Burtin (2009) Critical Care Medicine
Cader (2010) Journal of Physiotherapy
Cantaluppi (2008) Intensive Care Medicine
Cohen (2009) Critical Care (London, England)
Constantin (2010) Critical Care (London, England
Hochreiter (2009) Critical Care (London, England)
Loisa (2007) Critical Care (London, England)
Moraes (2009) Jornal de Pediatria
Olson (2009) Neurocritical Care
Perez-Barcena (2008) Nutrition
Pichamuthu (2010) Clinical Toxicology
Robinson (2010) Critical Care (London, England)
Shariatpanahi (2010) Journal of Critical Care

Appendix 3: Sample size changes

Registered pre-enrolment

Sample size not changed

Anderson (2008) Lancet Neurology
Investigators (2009) New England Journal of Medicine
Jansen (2010) American Journal of Respiratory & Critical Care Medicine
Jones (2010) JAMA
Papazian (2010) New England Journal of Medicine

Sample size changed

Barraud 2010
Initial *n* registered 740 in July 2005. Stopped for futility at 167 patients
Beale 2008
Registry states 52 patients anticipated (same as published paper), but paper states 344 patients initially estimated to be required
Cheung 2010
Registry states 180 patients. Changed to 20 patients in published paper due to apparent enrolment challenges
Endre 2010
Initial *n* registered 100 patients Feb 2006. Changed to 130 in registry. Final paper reports on 163 patients (no explanation)
Figueroa-Casas 2010
Initial *n* registered 224 patients Nov 2006. Final paper reports on 118 patients
Naidech 2010
No sample size in original registration, but then $n = 20$ listed in registry in 2010; $n = 6$ in Sept 2010. Final paper $n = 6$
Nobre 2008
Initial *n* registered 70 patients Nov 2005. Final paper reports on 79 (>10 % difference so classified as change). Registry changed after study completed
Roquilly 2011
No sample size in original registration Sept 2006; changed in registry from 180 to 150 in April 2010. Final paper 150 patients
Rose 2008
Registry anticipated 222 patients. Final paper reports on 102 patients
Timsit 2009
Initial registry $n = 2{,}000$ Dec 200; registry changed to $n = 1{,}600$ April 2008. Final paper $n = 1{,}636$
Van Eijk 2010
Changed in registry from $n = 440$ (2008) to $n = 104$ (2010)
Final paper $n = 109$. Stopped early for harm

Sample size change unclear

Bouadma 2010
No sample size listed in original registration, so considered to be a change. Sample size added to registry on 14 July 2008
Jabre 2009
Initial *n* registered 250 patients Feb 2007. Final paper reports on 655 patients. Unclear if changed; may have projected 400 (200 + 200 in 'subgroup of interest'), actually studied 465 patients
Meisel 2009
No sample size in original registration, but then listed in registry May 2011 after completion of enrolment
Strom 2010
No sample size in original registration April 2007
Final paper $n = 140$

Registered mid-enrolment

Sample size not changed

Azoulay (2010) American Journal of Respiratory & Critical Care Medicine
Dongelmans (2009) Anesthesia & Analgesia
Holzinger (2010) Diabetes Care
Investigators (2010) JAMA
Mentzelopoulos (2009) Archives of Internal Medicine
Morelli (2008) Critical Care (London, England)
Pieracci (2009) Surgical Infections

Sample size changed

Chung 2010
Initial *n* registered = 170 in July 2006; enrolment ended May 2009; changed to 62 in Dec 2010; reason in paper = stopped enrolment because increase need rescue in one arm). Possible harm
Frohmader 2010
Registry 100, paper 45—stopped early for (both) futility and slow recruitment
Gerovasili 2009
Registry 80 to 52, in Jan 2013. No reason

Appendix 3 continued

Gupta 2010
Registry 100, paper 53; study ran July 2006–Dec 2007; registered Aug 2007. No reason
Hernandez 2010
78 to 50 in Feb 2009. Reason stopped early for efficacy
Morelli 2009
Reg nil; reg 30–45 Feb 2008; paper 45
Ouellet 2009
Reg nil, then 80 (Mar 2008), then 22 in paper
Richir 2009
Reg 30, paper 21; could not recruit more
Routsi 2010
Reg 80 April 2009, stopped recruiting June 2009; 52 Jan 2013; final reg 52; paper 142 did randomize, but lost to follow-up
Walz 2010
Reg 680; July 2006 850; Jan 2013 960; paper 960
Xirouchi 2008
Reg 250; paper 208; enrolment (May 2006–March 2008) needed 100/arm—different to protocol

Sample size change unclear

Boerma 2012
Unclear: unsure when it appeared in registry; registration (Jun 2007) occurred midway through the study
Dubin 2010
Unclear: not in original registration; appears in reg. sometime later as 30, and in paper as 25
Holzinger 2011
Unclear: (registration—nil; then 66; registration in July 2007
Reade 2009
Unclear: nil registered at beginning, appears as 20 in reg and paper
Staudinger 2010
Unclear: reg—(enrolled from Sep 2005–April 2008; June 2008 150; 150 paper)

Registered post enrolment

Sample size not changed

Arcangeli (2010) Thrombosis Research
Barbosa (2010) Critical Care
Blaha (2009) Diabetes Care
Burtin (2009) Critical Care Medicine
Cader (2010) Journal of Physiotherapy
Cantaluppi (2008) Intensive Care Medicine
Cohen (2009) Critical Care (London, England)
Hochreiter (2009) Critical Care (London, England)
Loisa (2007) Critical Care (London, England)
Moraes (2009) Jornal de Pediatria
Pichamuthu (2010) Clinical Toxicology
Shariatpanahi (2010) Journal of Critical Care

Sample size changed

Perez-Barcena (2008)
Reg 43 on November 2010. Paper 30
Robinson (2010)
Reg 80 on February 2010. Paper 72. Stated in the paper reason: (we included 80 patients in the trial; eight were transferred before they could participate. The remaining 72 patients were randomized and treated according to the intent-to-treat principle

Appendix 3 continued

Sample size change unclear

Constantin (2010)
Unsure when it appeared in registry. Appears as 40 in final registry. Paper 44
Olson (2009)
Unsure when it appeared in registry. Appears as 67 in final registry. Paper 67

Appendix 4: Primary outcome changes

Registered pre-enrolment

Primary outcome not changed

Bouadma (2010) Lancet
Cheung (2010) Critical Care & Resuscitation
Figueroa-Casas (2010) Respiratory Care
Investigators (2009) New England Journal of Medicine
Jansen (2010) American Journal of Respiratory & Critical Care Medicine
Jones (2010) JAMA
Naidech (2010) Neurocritical Care
Nobre (2008) American Journal of Respiratory & Critical Care Medicine
Rose (2008) Intensive Care Medicine
Strom (2010) Lancet
Timsit (2009) JAMA

Primary outcome changed

Anderson (2008) Lancet Neurology
Initial reg. Sept 2005: Combination death and dependency, according to a 3–6 score on the mRS, at 3 months; paper: proportional change or growth in haematoma volume during the first 24 h after randomization
Barraud (2010) Intensive Care Medicine
Initial reg. July 2005: ICU mortality rate; reg. Sept 2010: ICU mortality rate, time frame 28 days; paper: 28-day mortality
Beale (2008) Critical Care Medicine
Initial reg. Dec 2005: organ dysfunction assessed by daily total SOFA score and by the delta total daily SOFA score. Study hypothesis states 5-day time frame; paper: organ dysfunction evolution assessed by daily total SOFA and delta daily total SOFA score over a study period of maximum 10 days
Endre (2010) Kidney International
Initial reg. Feb 2006: achieved plasma creatinine levels 7 days after randomization; paper: relative average value of creatinine
Jabre (2009) Lancet
Initial reg. Feb 2007. Maximal value of SOFA in the first 48 h of hospitalization; changed July 2008 in reg: maximal value of SOFA at the end of day 2; paper: maximum SOFA score during the first 3 days in the intensive care unit
Papazian (2010) New England Journal of Medicine
Initial reg. Mar 2006: reduction of the mortality rate of ARDS patients at 90 days; paper: death before hospital discharge and within 90 days of enrolment

Appendix 4 continued

van Eijk (2010) Lancet
Initial reg. Jun 2008: duration of delirium (time frame end of delirium); reg. April 2009: duration of delirium (time frame 3 months); paper: duration of delirium during hospital admission

SOFA Sepsis-related Organ Failure Assessment

Primary outcome unclear

Meisel (2009) American Journal of Respiratory & Critical Care Medicine
Initial reg. Nov 2005: none listed; reg. changed May 2011 to mHLA-DR expression >15,000 molecules per cell at study day 9; paper: mHLA-DR expression. Study ran Nov 2005–Jan 2007
Roquilly (2011) JAMA
Initial reg. Sep 2006: none listed; reg. changed Nov 2007 to incidence of nosocomial pneumopathy: radiological, clinical, and bacteriological criteria, time frame 28 days; paper: occurrence of hospital-acquired pneumonia within 28 days of randomization. Study ran Nov 2006 to Aug 2009

Registered mid-enrolment

Primary outcome not changed

Azoulay (2010) American Journal of Respiratory & Critical Care Medicine
Boerma (2010) Critical Care Medicine
Chung (2010) Critical Care Medicine
Dongelmans (2009) Anesthesia & Analgesia
Dubin (2010) Journal of Critical Care
Frohmader (2010) American Journal of Critical Care
Gerovasili (2009) Critical Care (London, England)
Gupta (2010) Respiratory Care
Holzinger (2010) Diabetes Care
Holzinger (2011) Critical Care Medicine
Reade (2009) Critical Care (London, England)
Richir (2009) Pharmalogical Research
Routsi (2010) Critical Care (London, England)
Staudinger (2010) Critical Care Medicine
Walz (2010) Critical Care Medicine

Primary outcome changed

Investigators (2010) JAMA
Initial reg. 2006—hospital mortality; June 2008 hospital mortality capped at 180 days; paper: hospital or 90-day mortality
Mentzelopoulos (2009) Archives of Internal Medicine
Reg. Dec 2006 + survival to discharge or home of facility as well as ROC; reg Dec 2008 + survival to discharge (d/c) or home of facility as well as ROC + adds time of 60 days; paper: ROC and survival to hospital d/c at 60 days

Appendix 4 continued

Morelli (2008) Critical Care (London, England)
Reg Mar 2008 hemodynamics 8 h; paper vasoactives
Morelli (2009) Critical Care (London, England)
Reg May 2007 systemic hemodynamics; paper: vasoactives
Pieracci (2009) Surgical Infections
Many primaries in registry (including mortality); a different one—haematocrit in paper
Xirouchaki (2008) Intensive Care Medicine
Registered = PAV success or sedation doses; paper = proportion of patients meeting failure during 48 h

Primary outcome unclear

Hernandez (2010) Chest
Registry Nov 2007 ETT/hosp; Feb 2009 ETT/1 month; paper ETT/unclear
Ouellet (2009) The American Journal of Surgery
Reg: rate of resp distress, Sept 2007, paper mentions goal only

ETT Endotracheal Tube Time

Registered post-enrolment

Primary outcome not changed

Arcangeli (2010) Thrombosis Research
Barbosa (2010) Critical Care
Blaha (2009) Diabetes Care
Burtin (2009) Critical Care Medicine
Cader (2010) Journal of Physiotherapy
Cohen (2009) Critical Care (London, England)
Constantin (2010) Critical Care (London, England)
Hochreiter (2009) Critical Care (London, England)
Loisa (2007) Critical Care (London, England)
Moraes (2009) Jornal de Pediatria
Olson (2009) Neurocritical Care
Perez-Barcena (2008) Nutrition
Pichamuthu (2010) Clinical Toxicology
Robinson (2010) Critical Care (London, England)

Primary outcome changed

Cantaluppi (2008) Intensive Care Medicine
The original registry entry (June 2007): reducing need for renal replacement therapy. Paper endpoint: viability of renal cell cultures
Shariatpanahi (2010) Journal of Critical Care
The original registry entry (August 2009): oxygenation, respiratory mechanics, serum inflammatory factors. Paper endpoint: delayed gastric emptying, developing ventilator-associated pneumonia, and clinical outcomes

Appendix 5: Registration information data

Journal name	Trial #	Registration date	Enrolment start	Enrolment end
Registered prior to enrolment				
Anderson (2008) Lancet Neurology	NCT00226096	September 2005	November 2005	April 2007
Barraud (2010) Intensive Care Medicine	NCT00122408	July 2005	February 2006	March 2008
Beale (2008) Critical Care Medicine	ISRCTN27438588	December 2005	January 2006	January 2008
Bouadma (2010) Lancet	NCT00472667	May 2007	June 2007	May 2008
Cheung (2010) Critical Care & Resuscitation	ACTRN012606000110583	March 2006	May 2006	October 2008
Endre (2010) Kidney International	ACTRN012606000058572	February 2006	March 2006	July 2008
Figueroa-Casas (2010) Respiratory Care	NCT00400881	November 2006	March 2007	September 2008
Investigators (2009) New England Journal of Medicine	NCT00221013	September 2005	December 2005	August 2008
Jabre (2009) Lancet	NCT00440102	February 2007	April 2007	February 2008
Jansen (2010) American Journal of Respiratory & Critical Care Medicine	NCT00270673	December 2005	February 2006	March 2008
Jones (2010) JAMA	NCT00372502	September 2006	January 2007	January 2009
Meisel (2009) American Journal of Respiratory & Critical Care Medicine	NCT00252915	November 2005	November 2005	January 2007
Naidech (2010) Neurocritical Care	NCT00727090	July 2008	August 2008	February 2009
Nobre (2008) American Journal of Respiratory & Critical Care Medicine	NCT00250666	November 2005	February 2006	April 2007
Papazian (2010) New England Journal of Medicine	NCT00299650	March 2006	March 2006	March 2008
Roquilly (2011) JAMA	NCT00563303	September 2006	November 2006	August 2009
Rose (2008) Intensive Care Medicine	ACTRN12605000265673	August 2005	January 2006	December 2006
Strom (2010) Lancet	NCT00466492	April 2007	April 2007	December 2008
Timsit (2009) JAMA	NCT00417235	December 2006	December 2006	June 2008
van Eijk (2010) Lancet	NCT00704301	June 2008	November 2008	January 2010
Registered during enrolment				
Azoulay (2010) American Journal of Respiratory & Critical Care Medicine	NCT00248443	November 2005	September 2005	November 2007
Boerma (2010) Critical Care Medicine	NCT00493415	June 2007	January 2007	June 2008
Chung (2010) Critical Care Medicine	NCT00351741	July 2006	April 2006	May 2009
Dongelmans (2009) Anesthesia & Analgesia	ISRCTN65935865	December 2005	October 2005	July 2006
Dubin (2010) Journal of Critical Care	NCT00799916	November 2008	January 2006	August 2009
Frohmader (2010) American Journal of Critical Care	ACTRN12605000167662	August 2005	July 2005	October 2006
Gerovasili (2009) Critical Care (London, England)	NCT00882830	April 2009	September 2007	June 2009
Gupta (2010) Respiratory Care	NCT00510991	August 2007	July 2006	December 2007

Appendix 5 continued

Journal name	Trial #	Registration date	Enrolment start	Enrolment end
Hernandez (2010) Chest	NCT00557752	November 2007	September 2005	June 2008
Holzinger (2010) Diabetes Care	NCT00494078	June 2007	June 2006	August 2008
Holzinger (2011) Critical Care Medicine	NCT00500851	July 2007	May 2007	February 2009
Investigators (2010) JAMA	NCT00320099	April 2006	January 2006	January 2009
Mentzelopoulos (2009) Archives of Internal Medicine	NCT00411879	December 2006	June 2006	March 2007
Morelli (2008) Critical Care (London, England)	NCT00639015	March 2008	December 2007	July 2008
Morelli (2009) Critical Care (London, England)	NCT00481572	May 2007	January 2007	January 2008
Ouellet (2009) The American Journal of Surgery	NCT00530725	September 2007	August 2006	April 2008
Pieracci (2009) Surgical Infections	NCT00450177	March 2007	January 2006	December 2007
Reade (2009) Critical Care (London, England)	NCT00505804	July 2007	April 2006	August 2008
Richir (2009) Pharmalogical Research	NCT00409097	December 2006	January 2006	December 2007
Routsi (2010) Critical Care (London, England)	NCT00882830	April 2009	September 2007	June 2009
Staudinger (2010) Critical Care Medicine	NCT00529776	September 2007	September 2005	April 2008
Walz (2010) Critical Care Medicine	NCT00288418	February 2006	December 2005	July 2007
Xirouchaki (2008) Intensive Care Medicine	ISRCTN00104615	September 2006	May 2006	March 2008
Registered after enrolment				
Arcangeli (2010) Thrombosis Research	NCT00890214	April 2009	September 2007	May 2008
Barbosa (2010) Critical Care	ISRCTN89432944	November 2009	March 2007	December 2007
Blaha (2009) Diabetes Care	NCT00764712	October 2008	February 2008	April 2008
Burtin (2009) Critical Care Medicine	NCT00695383	June 2008	December 2005	February 2007
Cader (2010) Journal of Physiotherapy	NCT00922493	June 2009	December 2007	November 2008
Cantaluppi (2008) Intensive Care Medicine	NCT00490477	June 2007	January 2006	April 2007
Cohen (2009) Critical Care (London, England)	ISRCTN16080446	September 2008	October 2006	April 2008
Constantin (2010) Critical Care (London, England)	NCT01014299	November 2009	September 2007	September 2008
Hochreiter (2009) Critical Care (London, England)	ISRCTN10288268	February 2009	January 2006	March 2007
Loisa (2007) Critical Care (London, England)	ISRCTN98820688	September 2006	July 2005	April 2006
Moraes (2009) Jornal de Pediatria	NCT00549809	October 2007	October 2005	June 2007
Olson (2009) Neurocritical Care	NCT00538369	October 2007	November 2006	September 2007
Perez-Barcena (2008) Nutrition	NCT01250080	November 2010	October 2005	October 2006
Pichamuthu (2010) Clinical Toxicology	ISRCTN84835351	January 2009	November 2007	December 2008
Robinson (2010) Critical Care (London, England)	ISRCTN03037804	February 2010	February 2006	March 2009
Shariatpanahi (2010) Journal of Critical Care	NCT00958685	August 2009	September 2007	August 2008

Appendix 6: Sample size data

Journal name	Published '*n*'	'*n*' at time of registration	Any changes in registry (date)	Final '*n*' recorded in registry (date)
Registered prior to enrolment				
Anderson (2008) Lancet Neurology	404	400	No changes	404
Barraud (2010) Intensive Care Medicine	167	740	No changes	740
Beale (2008) Critical Care Medicine	50	52	No changes	
Bouadma (2010) Lancet	621	Not listed	No changes	630 (2008)
Cheung (2010) Critical Care & Resuscitation	20	180	No changes	180
Endre (2010) Kidney International	163	100	130	130
Figueroa-Casas (2010) Respiratory Care	118	224	No changes	
Investigators (2009) New England Journal of Medicine	1,508	1,500	No changes	1508
Jabre (2009) Lancet	655	250	646 (2007)	656 (2008)
Jansen (2010) American Journal of Respiratory & Critical Care Medicine	348	350	No changes	350
Jones (2010) JAMA	300	300	No changes	300
Meisel (2009) American Journal of Respiratory & Critical Care Medicine	38	None listed	No changes	38
Naidech (2010) Neurocritical Care	6	None listed	20 (2010)	6
Nobre (2008) American Journal of Respiratory & Critical Care Medicine	79	70	No changes	70
Papazian (2010) New England Journal of Medicine	340	340	No changes	340
Roquilly (2011) JAMA	150	None listed	180 (2009)	150

Appendix 6 continued

Journal name	Published '*n*'	'*n*' at time of registration	Any changes in registry (date)	Final '*n*' recorded in registry (date)
Rose (2008) Intensive Care Medicine	102	222	No changes	
Strom (2010) Lancet	140	None listed	No changes	140
Timsit (2009) JAMA	1,636	2,000	1,600 (2008)	1,600
van Eijk (2010) Lancet	109	None listed	440 (2008)	104
Registered during enrolment				
Azoulay (2010) American Journal of Respiratory & Critical Care Medicine	219	206	No changes	206
Boerma (2010) Critical Care Medicine	70	Not Listed	No changes	70
Chung (2010) Critical Care Medicine	62	170	62 (2010)	62
Dongelmans (2009) Anesthesia & Analgesia	128	128	No changes	128
Dubin (2010) Journal of Critical Care	25	None listed	No changes	30
Frohmader (2010) American Journal of Critical Care	45	100	No changes	100
Gerovasili (2009) Critical Care (London, England)	49	80	No changes	80
Gupta (2010) Respiratory Care	53	None listed	No changes	100
Hernandez (2010) Chest	50	None listed	78 (2009)	50
Holzinger (2010) Diabetes Care	124	120	No changes	120
Holzinger (2011) Critical Care Medicine	66	None listed	No changes	66
Investigators (2010) JAMA	509	508	No changes	508
Mentzelopoulos (2009) Archives of Internal Medicine	100	100	No changes	100
Morelli (2008) Critical Care (London, England)	32	30	32 (2008)	32
Morelli (2009) Critical Care (London, England)	45	30	45 (2008)	45
Ouellet (2009) The American Journal of Surgery	22	None listed	80 (2008)	80
Pieracci (2009) Surgical Infections	200	200	No changes	200
Reade (2009) Critical Care (London, England)	20	None listed	No changes	20
Richir (2009) Pharmalogical Research	21	30	No changes	30
Routsi (2010) Critical Care (London, England)	142	80	No changes	80
Staudinger (2010) Critical Care Medicine	150	None listed	150 (2008)	150
Walz (2010) Critical Care Medicine	960	680	850 (2006)	850
Xirouchaki (2008) Intensive Care Medicine	208	250	No changes	208
*Registered after enrolmen*t				
Arcangeli (2010) Thrombosis Research	23	23	No changes	23
Barbosa (2010) Critical Care	23	25	No changes	25
Blaha (2009) Diabetes Care	120	120	No changes	120
Burtin (2009) Critical Care Medicine	90	90	No changes	90
Cader (2010) Journal of Physiotherapy	41	Not listed	No changes	Not listed
Cantaluppi (2008) Intensive Care Medicine	16		No changes	16
Cohen (2009) Critical Care (London, England)	180	180	No changes	180
Constantin (2010) Critical Care (London, England)	44	None	No changes	40
Hochreiter (2009) Critical Care (London, England)	110	110	No changes	110
Loisa (2007) Critical Care (London, England)	48	48	No changes	48
Moraes (2009) Jornal de Pediatria	165	70	No changes	70
Olson (2009) Neurocritical Care	67	Not listed	No changes	67
Perez-Barcena (2008) Nutrition	30	43	No changes	43
Pichamuthu (2010) Clinical Toxicology	60	60	No changes	None listed
Robinson (2010) Critical Care (London, England)	72	80	No changes	80
Shariatpanahi (2010) Journal of Critical Care	32	32	No changes	32

Appendix 7: Primary outcome data

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Registered prior to enrolment				
Anderson (2008) Lancet Neurology	The primary efficacy endpoint was the proportional change or growth in haematoma volume during the first 24 h after randomization	Combination death and dependency, according to a 3–5 score on the mRS, at 3 months (July 2007)	Measure: combination death and dependency, according to a 3–6 scores on the modified Rankin score. Time frame 3 months (July 2007)	Measure: combination death and dependency, according to a 3–6 scores on the modified Rankin score. Time frame: 3 months (July 2007)
Barraud (2010) Intensive Care Medicine	Primary endpoint was 28-day mortality	ICU mortality rate (July 2005)	Intensive care unit (ICU) mortality rate [time frame 28 days] [designated as safety issue: no] (September 2010)	ICU mortality rate [time frame: 28 days] [designated as safety issue: no] (September 2010)
Beale (2008) Critical Care Medicine	The primary endpoint was organ dysfunction evolution assessed by daily total SOFA and delta daily total SOFA score over a study period of maximum 10 days	Organ dysfunction assessed by daily total SOFA score and by the delta total daily SOFA score (significant reduction). Variables for organ dysfunction (worse parameter per day). (Note: study hypothesis states 5-day time frame)		
Bouadma (2010) Lancet	Primary endpoints were death from any cause by days 28 and 60, and number of days without antibiotics at 28 days after inclusion	Exposition to antibiotics, defined by antibiotic-free days [time frame: assessed 28 days after inclusion] Mortality [time frame: at day 28 and day 60] (May 2007)	None noted	Exposition to antibiotics, defined by antibiotic-free days [time frame: assessed 28 days after inclusion] [designated as safety issue: yes] mortality [time frame: at day 28 and day 60] [designated as safety issue: no] (July 2008)
Cheung (2010) Critical Care & Resuscitation	ICU and hospital LOS and change in composite scores for satisfaction with quality of care of families, intensivists, and bedside nursing staff	Composite score for overall patient/family satisfaction Time point: outcomes are measured at time of patient's death, or time of patient's discharge from ICU Primary outcome 2: composite score of staff satisfaction Time point: outcomes are measured at time of patients death, or time of patient's discharge from ICU Primary outcome 3: length of ICU stay Time point: outcomes are measured at time of patient's death, or time of patient's discharge from ICU Primary outcome 4: length of hospital stay Time point: outcomes are measured at time of patient's death, or time of patient's discharge from ICU (March 2006)	None noted	Composite score for overall patient/family satisfaction Time point: outcomes are measured at time of patients death, or time of patient's discharge from ICU Primary outcome 2: composite score of staff satisfaction Time point: outcomes are measured at time of patient's death, or time of patient's discharge from ICU Primary outcome 3: length of ICU stay Time point: outcomes are measured at time of patients death, or time of patient's discharge from ICU Primary outcome 4: length of hospital stay Time point: outcomes are measured at time of patients death, or time of patient's discharge from ICU (March 2006)

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Endre (2010) Kidney International	The prospectively defined primary outcome was the RAVC	The achieved plasma creatinine levels Time point: 7 days after randomization (Feb 2006)	None listed	Relative average value of plasma creatinine levels Time point: 7 days after randomization
Figueroa-Casas (2010) Respiratory Care	The primary outcome was duration of weaning (days from first SBT to extubation)	Duration of weaning time Incidence of reintubation		Duration of weaning time [time frame: days] [designated as safety issue: no] Weaning time was determined as number of days from the day of the first SBT to the day of extubation. All patients were followed until extubation
Investigators (2009) New England Journal of Medicine	The primary study outcome was death from any cause within 90 days after randomization	Death from all causes at 90 days after randomization (September 2005)	Death from all causes at 90 days after randomization. [Time frame: within 90 days after randomization] [designated as safety issue: no] (February 2009)	Death from all causes at 90 days after randomization. [Time frame, within 90 days after randomization] [designated as safety issue: no] (February 2009)
Jabre (2009) Lancet	The primary endpoint was the maximum SOFA score during the first 3 days in the ICU	Maximal value of the SOFA in the first 48 h of hospitalization (February 2007)	Maximal value of the SOFA [time frame: at the end of day 2] [designated as safety issue: yes] (July 2008)	Maximal value of SOFA [time frame: at the end of day 2] [designated as safety issue: yes] (July 2008)
Jansen (2010) American Journal of Respiratory & Critical Care Medicine	In-hospital mortality	In-hospital mortality (December 2005)	In-hospital mortality (January 2007)	In-hospital mortality (January 2007)
Jones (2010) JAMA	The primary endpoint was absolute in-hospital mortality rate	In-hospital mortality (September 2006)	Mortality [time frame: in-hospital] [designated as safety issue: no] (December 2007)	Mortality [time frame: in-hospital] [designated as safety issue: no] (December 2007)
Meisel (2009) American Journal of Respiratory & Critical Care Medicine	The primary outcome measure was mHLA-DR expression	None listed	None listed	Reconstitution of monocytic immunity as defined as a mHLA-DR expression greater than 15,000 molecules per cell at study day 9 [time frame: after therapy] [designated as safety issue: no] (May 2011)
Naidech (2010) Neurocritical Care	For statistical analysis, the primary study outcome was change in serum sodium at 6, 12, 18, 24, 36, and 48 h after enrolment	Change in serum sodium at 6, 12, 18, 24, 26, and 48 h [time frame: 48 h] [designated as safety issue: yes] (July 2008)	Change in serum sodium from baseline to 6 h [time frame: 48 h] [designated as safety issue: yes] (September 2010)	Change in serum sodium from baseline to 6 h [time frame: 48 h] [designated as safety issue: yes] (September 2010)
Nobre (2008) American Journal of Respiratory & Critical Care Medicine	The primary endpoint was systemic antibiotic exposure, measured using three variables	Exposure to systemic antimicrobial treatment (in duration of antibiotic treatment and total antibiotic exposure) (November 2005)	None listed	Exposure to systemic antimicrobial treatment (in duration of antibiotic treatment and total antibiotic exposure) (November 2005)
Papazian (2010) New England Journal of Medicine	The primary outcome was the proportion of patients who died before hospital discharge and within 90 days after study enrolment (the 90-day mortality)	Reduction of the mortality rate of ARDS patients at day 90 (March 2006)	Changed October 2008: reduction of the mortality rate of ARDS patients at day 90 [time frame: 36 months] [designated as safety issue: yes] (October 2008)	Changed October 2008: reduction of the mortality rate of ARDS patients at day 90 [time frame: 36 months] [designated as safety issue: yes] (October 2008)

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Roquilly (2011) JAMA	The study's primary outcome was occurrence of hospital-acquired pneumonia within 28 days of randomization	None listed	Incidence of nosocomial pneumopathy: radiological, clinical, and bacteriological criteria [time frame: 28 days] (November 2007)	Incidence of nosocomial pneumopathy: radiological, clinical, and bacteriological criteria [time frame: 28 days] [designated as safety issue: no] (April 2008)
Rose (2008) Intensive Care Medicine	The time to separation, defined as time in hours from randomization (immediately following successful completion of the 30-min spontaneous breathing PS test) to the time of declaration of "separation potential" was the primary outcome of interest	Time to readiness for separation (extubation)		Time to readiness for separation (extubation)
Strom (2010) Lancet	The primary outcome measure was the number of days without mechanical ventilation (after successful extubation, or removal of ventilator support for patients with tracheostomies) in a 28-day period	Time receiving mechanical ventilation, intensive care and hospital length of stay (April 2007)	Time receiving mechanical ventilation, total intensive care and hospital length of stay [designated as safety issue: no] (March 2010)	Time receiving mechanical ventilation, total intensive care and hospital length of stay [designated as safety issue: no] (March 2010)
Timsit (2009) JAMA	Major CRIs for comparison of CHGIS vs control dressings	Systemic catheter-related sepsis as defined by a blinded expert panel to unmask differences between chlorhexidine dressings and no chlorhexidine dressings Significant catheter culture $\geq$103 cfu/ml for noninferiority between 7-day and 3-day catheter-dressing frequencies (December 2006)	Systemic catheter-related sepsis as defined by a blinded expert panel to unmask differences between chlorhexidine dressings and no chlorhexidine dressings [time frame: 48 h] [designated as safety issue: no] Significant catheter culture $\geq$103 cfu/ml for noninferiority between 7-day and 3-day catheter-dressing frequencies [time frame: 48 h] [designated as safety issue: no] (April 2008)	Systemic catheter-related sepsis as defined by a blinded expert panel to unmask differences between chlorhexidine dressings and no chlorhexidine dressings [time frame: 48 h] [designated as safety issue: no] Significant catheter culture $\geq$103 cfu/ml for noninferiority between 7-day and 3-day catheter-dressing frequencies [time frame: 48 h] [designated as safety issue: no] (April 2008)
van Eijk (2010) Lancet	The primary outcome was the duration of delirium during hospital admission (i.e. in the ICU and in the hospital ward combined)	Duration of delirium [time frame: end of delirium] [designated as safety issue: no] (June 2008)	None listed	Duration of delirium [time frame: 3 months] [designated as safety issue: no] (April 2009)
Registered during enrolment				
Azoulay (2010) American Journal of Respiratory & Critical Care Medicine	The primary endpoint was the intubation rate	Reduction in intubation rate (November 2005)	Reduction in intubation rate [time frame: 28 days] [designated as safety issue: yes] (Feb 2011)	Reduction in intubation rate [time frame: 28 days] [designated as safety issue: yes] (Feb 2011)
Boerma (2010) Critical Care Medicine	The primary endpoint was MFI within the 24-h study medication period	Increase of MFI by nitroglycerine [time frame: 2 years] (June 2007)	None noted	Increase of MFI by nitroglycerine [time frame: 2 years] [designated as safety issue: no] (May 2008)

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Chung (2010) Critical Care Medicine	The primary endpoint was ventilator-free days in the first 28 days, defined as the number of days after randomization from day 0 to day 28 alive without ventilator assistance for at least 48 consecutive hours	To assess differences in ventilator-free days during the first 28 days between two ventilator strategies (July 2006)	Ventilator-free days during the first 28 days [time frame: 28 days] [designated as safety issue: no] The primary endpoint was ventilator-free days in the first 28 days, defined as the number of days after randomization from day 0 to day 28 alive without ventilator assistance for at least 48 consecutive hours (November 2010)	Ventilator-free days during the first 28 days [time frame: 28 days] [designated as safety issue: no] The primary endpoint was ventilator-free days in the first 28 days, defined as the number of days after randomization from day 0 to day 28 alive without ventilator assistance for at least 48 consecutive hours (November 2010)
Dongelmans (2009) Anesthesia & Analgesia	The primary endpoint of this study was time until tracheal extubation	Number of ABG analyses Number of audible alarms Number of manual changes in the ventilator settings, including: Switches from PC to PS (only in the control group) Changes in minute ventilation (only in the ASV group) Lowering of PS level (only in the control group) Duration of period of spontaneous mechanical ventilation Duration of total period of tracheal intubation		Number of ABG analyses Number of audible alarms Number of manual changes in the ventilator settings, including: Switches from PC to PS (only in the control group) Changes in minute ventilation (only in the ASV group) Lowering of PS level (only in the control group) Duration of period of spontaneous mechanical ventilation Duration of total period of tracheal intubation
Dubin (2010) Journal of Critical Care	Sublingual capillary MFI	Sublingual microcirculation [time frame: 24 h] [designated as safety issue: no] (November 2008)	None listed	Sublingual microcirculation [time frame: 24 h] [designated as safety issue: no] (November 2008)
Frohmader (2010) American Journal of Critical Care	The primary outcome was frequency of liquid stool (mean number of episodes per patient per day)	A double blind randomized placebo-controlled intervention trial to determine the efficacy of the probiotic VSL #3 in reducing the incidence and/or frequency of diarrhoea in enterally fed critically ill patients		A double blind randomized placebo-controlled intervention trial to determine the efficacy of the probiotic VSL #3 in reducing the incidence and/or frequency of diarrhoea in enterally fed critically ill patients
Gerovasili (2009) Critical Care (London, England)	The aim of our study was to assess the effect of EMS on muscle mass preservation in critically ill patients with the use of US	Diagnosis of CIPNM [time frame: June 2009] [designated as safety issue: no] (April 2009)	None listed	Diagnosis of CIPNM [time frame: June 2009] [designated as safety issue: no] (April 2009)
Gupta (2010) Respiratory Care	Improvement in lung function (FEV1 increased by 50 % compared to admission), ICU stay, hospital stay	Improvement in lung function defined as an increase of at least 50 % in FEV1 as compared to baseline value on admission or an increase in FEV1 to greater than 60 % of predicted value [time frame: time to discharge] Intensive care unit length of stay [time frame: time to discharge] Hospital length of stay [time frame: time to discharge] (August 2007)	None listed	Improvement in lung function defined as an increase of at least 50 % in FEV1 as compared to baseline value on admission or an increase in FEV1 to greater than 60 % of predicted value [time frame: time to discharge] Intensive care unit length of stay [time frame: time to discharge] Hospital length of stay [time frame: time to discharge] (August 2007)

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Hernandez (2010) Chest	The primary endpoint was intubation rate	Intubation rate [time frame: hospital stay] (November 2007)	None listed	Intubation rate [time frame: 1 month] [designated as safety issue: no] (February 2009)
Holzinger (2010) Diabetes Care	The primary endpoint, percentage of time at 110 mg/dl	Percentage of time of normoglycaemia, defined as glucose levels below 110 mg/dl, during the study period [time frame: 72 h] (June 2007)	Percentage of time of normoglycaemia, defined as glucose levels below 110 mg/dl, during the study period [time frame: 72 h] [designated as safety issue: no] (December 2007)	Percentage of time of normoglycaemia, defined as glucose levels below 110 mg/dl, during the study period [time frame: 72 h] [designated as safety issue: no] (December 2007)
Holzinger (2011) Critical Care Medicine	The primary outcome was successful implantation of the tube	Success rate of jejunal placement [time frame: 24 h] (July 2007)	None listed	Success rate of jejunal placement [time frame: 24 h] [designated as safety issue: no] (February 2008)
Investigators (2010) JAMA	The primary outcome measure was in-hospital mortality (or 90-day mortality, whichever occurred first)	In-hospital mortality (April 2006)	In-hospital mortality [time frame: day 180] [designated as safety issue: yes] (June 2008)	In-hospital mortality [time frame: day 180] [designated as safety issue: yes] (June 2008)
Mentzelopoulos (2009) Archives of Internal Medicine	Primary endpoints were return of spontaneous circulation for 15 min or longer and survival to hospital discharge, defined as presence of an attending physician discharge order to home or to a rehabilitation facility	Survival to discharge either to home or to a rehabilitation facility. Return of spontaneous circulation for at least 15 min (December 2006)	(1) Return of spontaneous circulation for longer than 15 min and (2) survival to discharge either to home or to a rehabilitation facility. [Time frame: 60 days (actual)] [designated as safety issue: no] (July 2008)	(1) Return of spontaneous circulation for longer than 15 min and (2) survival to discharge either to home or to a rehabilitation facility. [Time frame: 60 days (actual)] [designated as safety issue: no] (July 2008)
Morelli (2008) Critical Care (London, England)	The main endpoint of the present study was the modifications of the PDR and CBI after phenylephrine administration as compared with the norepinephrine group	Systemic and regional hemodynamics [time frame: during the first 12 h from the onset of septic shock] [designated as safety issue: no] (March 2008)	None listed	Systemic and regional hemodynamics [time frame: during the first 12 h from the onset of septic shock] [designated as safety issue: no] (March 2008)
Morelli (2009) Critical Care (London, England)	The primary endpoint of the present study was the reduction of average open-label NE requirements in patients treated with TP as compared with the AVP or NE group	Systemic and regional hemodynamics [time frame: during the first 48 h from the onset of septic shock] (May 2007)	Systemic and regional hemodynamics [time frame: during the first 48 h from the onset of septic shock] [designated as safety issue: yes] (January 2008)	Systemic and regional hemodynamics [time frame: during the first 48 h from the onset of septic shock] [designated as safety issue: yes] (January 2008)
Ouellet (2009) The American Journal of Surgery	The primary goals of the OPTICC pilot study were to examine the safety and feasibility of conducting a fully powered noninferiority trial of the treatment of OPTXs in traumatized patients undergoing PPV	Outcome variables: in ventilated patients with small to moderate sized OPTXs, the rate of respiratory distress will not differ between those treated with tube thoracostomy tubes and those not treated but simply observed		Outcome variables: in ventilated patients with small to moderate sized OPTXs, the rate of respiratory distress will not differ between those treated with tube thoracostomy tubes and those not treated but simply observed

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Pieracci (2009) Surgical Infections	Power analysis was conducted on the basis of the primary outcome of difference in haematocrit, computed at enrolment and weekly thereafter	Weekly haemoglobin, days 0–42 Weekly serum iron concentration, days 0–42 Weekly serum ferritin concentration, days 0–42 Weekly erythrocyte zinc protoporphyrin concentration, days 0–42 Blood transfusion Infection Drug-related constipation Drug-related nausea/vomiting ICU mortality Hospital mortality (March 2007)	None listed	Weekly haemoglobin, days 0–42 Weekly serum iron concentration, days 0–42 Weekly serum ferritin concentration, days 0–42 Weekly erythrocyte zinc protoporphyrin concentration, days 0–42 Blood transfusion Infection Drug-related constipation Drug-related nausea/vomiting ICU mortality Hospital mortality (March 2007)
Reade (2009) Critical Care (London, England)	The primary endpoint was time from the commencement of study drug to extubation	Time from the commencement of treatment to extubation (July 2007)	Not listed	Time from the commencement of treatment to extubation (July 2007)
Richir (2009) Pharmalogical Research	Unclear	ADMA concentration		ADMA concentration
Routsi (2010) Critical Care (London, England)	The primary endpoint was the diagnosis of CIPNM as assessed with the MRC scale for muscle strength	Diagnosis of CIPNM [time frame: June 2009] [designated as safety issue: no] (April 2009)	Not listed	Diagnosis of CIPNM [time frame: June 2009] [designated as safety issue: no] (April 2009)
Staudinger (2010) Critical Care Medicine	The primary endpoint was occurrence of VAP	VAP		VAP
Walz (2010) Critical Care Medicine	The primary antimicrobial outcome was a dichotomous measure that classified CC as positive (15 cfu) or negative (15 cfu)	Incidence of catheter colonization (February 2006)	None listed	Incidence of catheter colonization (February 2006)
Xirouchaki (2008) Intensive Care Medicine	The primary endpoint was the proportion of patients meeting failure criteria in each mode during the 48-h study period	PAV success rate Sedation doses		
Registered after enrolment				
Arcangeli (2010) Thrombosis Research	Platelet responsiveness	Context and purpose of the study: prospective, randomized comparison of a PGIA versus UFH as circuit anticoagulant. Platelet responsiveness was assessed from peripheral blood by LTA induced by collagen and ADP, at baseline, 4 and 24 h after treatment onset. Platelet function was also assessed in blood samples collected in the circuit before and after the filter		Context and purpose of the study: prospective, randomized comparison of a PGIA versus UFH as circuit anticoagulant. Platelet responsiveness was assessed from peripheral blood by LTA induced by collagen and ADP, at baseline, 4 and 24 h after treatment onset. Platelet function was also assessed in blood samples collected in the circuit before and after the filter

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Barbosa (2010) Critical Care	The outcomes were plasma phospholipid fatty acid profile, inflammatory mediators in plasma and produced by LPS-stimulated whole blood, routine biochemical and physiological markers, gas exchange, and clinical outcomes	Plasma phospholipid fatty acid status at days 0, 1, 2, and 6 Plasma inflammatory cytokines at days 0, 1, 2, and 6 Inflammatory cytokine production by endotoxin stimulated whole blood at days 0, 1, 2, and 6 Length of ICU and hospital stay (Nov 2009)	None noted	Plasma phospholipid fatty acid status at days 0, 1, 2, and 6 Plasma inflammatory cytokines at days 0, 1, 2, and 6 Inflammatory cytokine production by endotoxin stimulated whole blood at days 0, 1, 2, and 6 Length of ICU and hospital stay (Nov 2009)
Blaha (2009) Diabetes Care	Effectiveness of different TGC management protocols	The effectiveness of different TGC management protocols [time frame: ICU stay] [designated as safety issue: no]		The effectiveness of different TGC management protocols [time frame: ICU stay] [designated as safety issue: no]
Burtin (2009) Critical Care Medicine	The primary outcome was 6MWD as measured at hospital discharge	Six-minute walking distance [time frame: hospital discharge] [designated as safety issue: no]		Six-minute walking distance [time frame: hospital discharge] [designated as safety issue: no]
Cader (2010) Journal of Physiotherapy	MIP measured by using a vacuum manometer	Measurement of the MIP (June 2009)	None noted	Measurement of the MIP (June 2009)
Cantaluppi (2008) Intensive Care Medicine	The primary outcome variable was viability of renal cell cultures exposed to the plasma of septic patients	Verify whether LPS removal with PMX-B hemoperfusion protects from acute renal injury, reducing the need for RRT, in patients with severe sepsis from gram negative infection [time frame: up to 28 days] (21 June 2007)	Number of participants not requiring RRT [time frame: 28 days from the admission] (6 May 2010)	Number of participants not requiring RRT [time frame: 28 days from the admission] (6 May 2010)
Cohen (2009) Critical Care (London, England)	The primary outcome measure was successful extubation, defined as the ability to maintain spontaneous, unassisted breathing for longer than 48 h after removal of the endotracheal tube	Tolerance of the spontaneous breathing trial: ability to maintain spontaneous breathing for longer than 48 h after extubation (September 2008)	None noted	Tolerance of the spontaneous breathing trial: ability to maintain spontaneous breathing for longer than 48 h after extubation (September 2008)
Constantin (2010) Critical Care (London, England)	The primary endpoint was the PaO_2 value obtained 5 min after tracheal intubation	Oxygenation (PaO_2) measured 5 min after the onset of mechanical ventilation [time frame: 5 min after the onset of mechanical ventilation] [designated as safety issue: yes] (November 2009)	None noted	Oxygenation (PaO_2) measured 5 min after the onset of mechanical ventilation [time frame: 5 min after the onset of mechanical ventilation] [designated as safety issue: yes] (November 2009)
Hochreiter (2009) Critical Care (London, England)	Duration of antibiotic therapy	Duration of antibiotic therapy (February 2009)	None listed	Duration of antibiotic therapy. (February 2009)
Loisa (2007) Critical Care (London, England)	The primary endpoint in the study was the difference in the mean blood glucose levels between the study groups and the occurrence of hyper- and hypoglycaemic episodes	Mean blood glucose levels in study groups and the number of hyperglycaemic (more than 7 mmol/l) and hypoglycaemic (less than 3 mmol/l) episodes (September 2006)	None listed	Mean blood glucose levels in study groups and the number of hyperglycaemic (more than 7 mmol/l) and hypoglycaemic (less than 3 mmol/l) episodes (September 2006)

Appendix 7 continued

Journal name	Published outcome	Outcome registered at time of registration	Changes identified within the registry (date)	Final registration outcome (date)
Moraes (2009) Jornal de Pediatria	To compare mechanical ventilation support in IMV mode with SIMV + PS in terms of length of time on MV, time taken for weaning, and length of hospital stay	Duration of mechanical ventilation/ weaning and length of stay in PICU [time frame: 2 years] (October 2007)	Duration of mechanical ventilation/ weaning and length of stay in PICU [time frame: 2 years] [designated as safety issue: yes] (January 2008)	Duration of mechanical ventilation/ weaning and length of stay in PICU [time frame: 2 years] [designated as safety issue: yes] (January 2008)
Olson (2009) Neurocritical Care	The primary endpoint for this study was the total dose of sedative drug (propofol) used in 12 h	How much sedative was infused [time frame: length of stay]		How much sedative was infused [time frame: length of stay]
Perez-Barcena (2008) Nutrition	Unclear	Expression of TLR2 and TLR4 in peripheral blood monocytes was determined by flow cytometry		Expression of TLR2 and TLR4 in peripheral blood monocytes was determined by flow cytometry
Pichamuthu (2010) Clinical Toxicology	The primary clinical outcome was the incidence of intermediate syndrome	Lower the incidence of intermediate syndrome, measured during hospital stay and determined at discharge Reduce effective circulating organophosphate levels, assayed directly and functionally and measured directly after the infusion of trial or placebo interventions (January 2009)	None listed	Lower the incidence of intermediate syndrome, measured during hospital stay and determined at discharge Reduce effective circulating organophosphate levels, assayed directly and functionally and measured directly after the infusion of trial or placebo interventions (January 2009)
Robinson (2010) Critical Care (London, England)	The primary endpoint was peak anti-factor Xa levels	Peak anti-factor Xa levels (peak = 4 h post-enoxaparin administration). Levels of anti-factor Xa activity were determined using a validated chromogenic assay kit (COAMATIC Heparin, Chromogenix, Instrumentation Laboratory Company, Lexington, USA) with the substrate S-2732, and the apparatus (STA-R Evolution, Diagnostica Stago, Asnieres, France) (February 2010)	Not listed	Peak anti-factor Xa levels (peak = 4 h post-enoxaparin administration). Levels of anti-factor Xa activity were determined using a validated chromogenic assay kit (COAMATIC Heparin, Chromogenix, Instrumentation Laboratory Company, Lexington, USA) with the substrate S-2732, and the apparatus (STA-R Evolution, Diagnostica Stago, Asnieres, France) (February 2010)
Shariatpanahi (2010) Journal of Critical Care	Delayed gastric emptying, developing ventilator-associated pneumonia, and clinical outcomes	Changes in oxygenation, respiratory mechanics, and serum inflammatory factors [time frame: 21 days] [designated as safety issue: yes] Oxygenation [time frame: 21 days] [designated as safety issue: yes]		Changes in oxygenation, respiratory mechanics, and serum inflammatory factors [time frame: 21 days] [designated as safety issue: yes] Oxygenation [time frame: 21 days] [designated as safety issue: yes]

SOFA Sepsis-related Organ Failure Assessment, *LOS* length of stay, *SBT* spontaneous breathing trial, *PS* pressure support, *US* ultrasonography, *MRC* Medical Research Council, *VAP* ventilator-associated pneumonia, *cfu* colony-forming units, *ABG* arterial blood gas, *LTA* light-transmittance aggregometry, *MIP* maximal inspiratory pressure, *RRT* renal replacement therapy, *ARDS* acute respiratory distress syndrome, *LPS* lipopolysaccharide

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