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Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults (Review)

Yu Y, Zhang K, Zhang L, Zong H, Meng L, Han R

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TABLE OF CONTENTS

[Intervention Review]

Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults

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ABSTRACT

Background

Various techniques have been employed for the early detection of perioperative cerebral ischaemia and hypoxia. Cerebral near-infrared spectroscopy (NIRS) is increasingly used in this clinical scenario to monitor brain oxygenation. However, it is unknown whether perioperative cerebral NIRS monitoring and the subsequent treatment strategies are of benefit to patients.

Objectives

To assess the effects of perioperative cerebral NIRS monitoring and corresponding treatment strategies in adults and children, compared with blinded or no cerebral oxygenation monitoring, or cerebral oxygenation monitoring based on non-NIRS technologies, on the detection of cerebral oxygen desaturation events (CDEs), neurological outcomes, non-neurological outcomes and socioeconomic impact (including cost of hospitalization and length of hospital stay).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 12), Embase (1974 to 20 December 2016) and MEDLINE (PubMed) (1975 to 20 December 2016). We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing studies on 20 December 2016. We updated this search in November 2017, but these results have not yet been incorporated in the review. We imposed no language restriction.

Selection criteria

We included all relevant randomized controlled trials (RCTs) dealing with the use of cerebral NIRS in the perioperative setting (during the operation and within 72 hours after the operation), including the operating room, the postanaesthesia care unit and the intensive care unit.

Data collection and analysis

Two authors independently selected studies, assessed risk of bias and extracted data. For binary outcomes, we calculated the risk ratio (RR) and its 95% confidence interval (CI). For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. As we expected clinical and methodological heterogeneity between studies, we employed a random-effects model for analyses and we examined the data for heterogeneity (I^2 statistic). We created a 'Summary of findings' table using GRADEpro.

Main results

We included 15 studies in the review, comprising a total of 1822 adult participants. There are 12 studies awaiting classification, and eight ongoing studies.

None of the 15 included studies considered the paediatric population. Four studies were conducted in the abdominal and orthopaedic surgery setting (lumbar spine, or knee and hip replacement), one study in the carotid endarterectomy setting, and the remaining 10 studies in the aortic or cardiac surgery setting. The main sources of bias in the included studies related to potential conflict of interest from industry sponsorship, unclear blinding status or missing participant data.

Two studies with 312 participants considered postoperative neurological injury, however no pooled effect estimate could be calculated due to discordant direction of effect between studies (low-quality evidence). One study (N = 126) in participants undergoing major abdominal surgery reported that 4/66 participants experienced neurological injury with blinded monitoring versus 0/56 in the active monitoring group. A second study (N = 195) in participants having coronary artery bypass surgery reported that 1/96 participants experienced neurological injury in the blinded monitoring group compared with 4/94 participants in the active monitoring group.

We are uncertain whether active cerebral NIRS monitoring has an important effect on the risk of postoperative stroke because of the low number of events and wide confidence interval (RR 0.25, 95% CI 0.03 to 2.20; 2 studies, 240 participants; low-quality evidence).

We are uncertain whether active cerebral NIRS monitoring has an important effect on postoperative delirium because of the wide confidence interval (RR 0.63, 95% CI 0.27 to 1.45; 1 study, 190 participants; low-quality evidence).

Two studies with 126 participants showed that active cerebral NIRS monitoring may reduce the incidence of mild postoperative cognitive dysfunction (POCD) as defined by the original studies at one week after surgery (RR 0.53, 95% CI 0.30 to 0.95, I^2 = 49%, low-quality evidence).

Based on six studies with 962 participants, there was moderate-quality evidence that active cerebral oxygenation monitoring probably does not decrease the occurrence of POCD (decline in cognitive function) at one week after surgery (RR 0.62, 95% CI 0.37 to 1.04, I^2 = 80%). The different type of monitoring equipment in one study could potentially be the cause of the heterogeneity.

We are uncertain whether active cerebral NIRS monitoring has an important effect on intraoperative mortality or postoperative mortality because of the low number of events and wide confidence interval (RR 0.63, 95% CI 0.08 to 5.03, I^2= 0%; 3 studies, 390 participants; low-quality evidence). There was no evidence to determine whether routine use of NIRS-based cerebral oxygenation monitoring causes adverse effects.

Authors' conclusions

The effects of perioperative active cerebral NIRS monitoring of brain oxygenation in adults for reducing the occurrence of short-term, mild POCD are uncertain due to the low quality of the evidence. There is uncertainty as to whether active cerebral NIRS monitoring has an important effect on postoperative stroke, delirium or death because of the low number of events and wide confidence intervals. The conclusions of this review may change when the eight ongoing studies are published and the 12 studies awaiting assessment are classified. More RCTs performed in the paediatric population and high-risk patients undergoing non-cardiac surgery (e.g. neurosurgery, carotid endarterectomy and other surgery) are needed.

PLAIN LANGUAGE SUMMARY

Use of cerebral near-infrared spectroscopy (NIRS) for monitoring brain oxygenation during or after surgery in adults and children

The review question

We assessed the effects of monitoring the brain with cerebral near-infrared spectroscopy (NIRS), and treatments based on it, during and after surgery in adults and children. We aimed to determine whether NIRS detects reduced oxygen supply to the brain, which would allow the use of interventions to improve nervous system, mental process (cognition) and other outcomes that can have an impact on patients' hospital length of stay and costs.

Background

The human brain needs a lot of oxygen (has a high oxygen consumption) and is very sensitive to reduced oxygen supply. Successful treatment for low levels of oxygen in the brain during or after surgery relies on early diagnosis of a lack of oxygen. Cerebral NIRS is increasingly used for the early detection of lack of oxygen to the brain. It uses near-infrared light (700 to 1000 nanometres) to penetrate through the superficial layers of the head, including the scalp and the skull, to show the cerebral tissue.

Study characteristics

The evidence is current to December 2016. We updated our search in November 2017, but these results have not yet been incorporated in the review. We included 15 completed randomized controlled trials involving 1822 participants. There are 8 ongoing studies and 12 waiting further assessment.

None of the completed studies included infants or children. In four studies participants were undergoing abdominal or orthopaedic surgery, one study included participants undergoing a procedure to restore proper blood flow to the brain, and in the remaining 10 studies participants were undergoing large blood vessel or heart surgery with or without heart bypass. The studies all used cerebral NIRS in the operating room, with only two also using cerebral NIRS in the intensive care unit. The control groups were monitored using methods such as heart rate and mean arterial blood pressure, electroencephalogram, transcranial doppler, bispectral index, oxygen saturation in the jugular vein, evoked potentials or cerebral tissue oxygen partial pressure. Overall, the different studies varied in their approach to the review question.

Key results

We did not pool (combine) the data for the outcome postoperative neurological injury because of variations between studies. One study with 126 participants having major abdominal surgery reported that 4/66 versus 0/56 participants experienced neurological injury with blinded and active monitoring, respectively. A second study with 195 participants undergoing coronary artery bypass surgery reported that 1/96 versus 4/94 participants suffered neurological injury in the blinded (masked) and active (with active treatments) monitoring groups, respectively. We are unsure whether active NIRS monitoring has an important effect on the risk of postoperative stroke and delirium because there was a low number of events and the result was not precise (2 studies, 240 participants; 1 study, 190 participants, respectively; low-quality evidence). Based on two studies with 126 participants, we found low-quality evidence that cerebral NIRS monitoring may reduce the number of participants with mild cognitive impairment at one week after surgery. Based on six studies with 962 participants, we found moderate-quality evidence that monitoring with cerebral NIRS probably leads to little or no decrease in the number of participants with a decline in cognitive function one week after surgery. We are uncertain whether active cerebral oxygenation monitoring has a crucial effect on intraoperative or postoperative deaths because there was a low number of events and the result was not precise (3 studies, 390 participants; low-quality evidence). We did not find any detrimental effects of the routine use of NIRS-based brain oxygenation monitoring.

Quality of the evidence

Overall, it is uncertain whether active NIRS monitoring has a crucial effect on postoperative stroke, delirium or death because of the imprecision of the results (low-quality evidence). Therefore, the effects of active cerebral NIRS monitoring on postoperative nervous system injury, delirium, decline in cognitive function and death are uncertain. For some outcomes, such as postoperative stroke or other neurological injury, the evidence was based on few studies with limited numbers of participants. Reporting of outcomes was often incomplete for all study participants, as was reporting of the study design, such as blinding. Some studies had potential conflicts of interest from industry sponsorship.

Summary of findings for the main comparison. Active cerebral oxygenation monitoring compared to blinded cerebral oxygenation monitoring for perioperative monitoring of brain oxygenation in children and adults

Active cerebral oxygenation monitoring compared to blinded cerebral oxygenation monitoring for perioperative monitoring of brain oxygenation in children and adults

Patient or population: children and adults undergoing surgery
Settings: hospitals (in Canada, United States, United Kingdom, Croatia, Australia, South Africa, Turkey, Poland and Greece) during the perioperative period (including in the operating room and ICU) and hospital stay
Intervention: active cerebral oxygenation monitoring
Comparison: blinded cerebral oxygenation monitoring

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Blinded cerebral oxygenation monitoring	Active cerebral oxygenation monitoring				
Postoperative neurological injury **(follow-up: 1 week or hospital discharge)**	No pooled effect estimate available due to discordant direction of effect between studies. One study (N = 126) in people undergoing major abdominal surgery reported that 4/66 participants experienced neurological injury with blinded monitoring versus 0/56 in the active monitoring group. A second study (N = 195) in people having coronary artery bypass surgery reported that 1/96 participants experienced neurological injury in the blinded monitoring group compared with 4/94 participants in the active monitoring group.		Not estimable	312 (2 studies)	⊕⊕⊖⊖ **low**[1,3]	Very serious heterogeneity (I^2 = 72%)
Postoperative stroke **(follow-up: within 30 days)**	40 per 1000	10 per 1000 (1 to 88)	**RR 0.25** (0.03 to 2.20)	240 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	—
POD: postoperative delirium **(follow-up: 1 week)**	135 per 1000	85 per 1000 (37 to 196)	**RR 0.63** (0.27 to 1.45)	190 (1 study)	⊕⊕⊖⊖ **low**[1,2]	—
POCD defined by original studies - mild **(follow-up: 1 week)**	641 per 1000	340 per 1000 (192 to 609)	**RR 0.53** (0.30 to 0.95)	126 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	—

POCD: decline in cognitive function **(follow-up: 1 week)**	400 per 1000	248 per 1000 (148 to 416)	**RR 0.62** (0.37 to 1.04)	962 (6 studies)	⊕⊕⊕⊖ **moderate**[1]	—
Intraoperative mortality or postoperative mortality: Death **(follow-up: 30 days)**	10 per 1000	6 per 1000 (1 to 52)	**RR 0.63** (0.08 to 5.03)	390 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	—
Adverse events	See comments	See comments	Not estimable	See comments	See comments	None of the studies reported adverse effects caused by use of NIRS-based cerebral oxygenation monitoring

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **POCD:** postoperative cognitive dysfunction; **POD:** postoperative delirium; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Risk of bias: downgraded by one level because the body of evidence contained one or more of the following risks of bias: potential conflict of interest from industry sponsorship, unclear blinding status or missing participant data.
[2]Imprecision: downgraded by one level as the effect estimate included both appreciable benefit and appreciable harm, or the sample size is smaller than the optimal information size.
[3]Inconsistency: downgraded by one level as the statistical heterogeneity between studies was substantial.

BACKGROUND

Description of the condition

The human brain is one of the organs with high oxygen utilization; thus it is extremely susceptible to hypoxic conditions (Gale 2004; Stys 1998). The incidence of intraoperative decrease in cerebral oxygen saturation is about 40% to 70%, depending on the definition of cerebral oxygen desaturation events (CDEs) and the patient population (Fischer 2011; Greenberg 2013; Murkin 2007; Slater 2009; Yao 2004). The prevalence of immediate postoperative CDEs is approximately 50% (Greenberg 2013). Potential contributors to low cerebral regional oxygen saturation ($rScO_2$) include unstable haemodynamics, systemic desaturation, low haematocrit, hypocapnia, cardiac dysfunction, increased cerebral oxygen consumption, malposition of the head/cannula and specific surgical procedures such as deep hypothermic circulatory arrest and rewarming and aortic/carotid cross-clamping (Closhen 2013; Deschamps 2013; Harilall 2013; Hoffman 2004; Meng 2012; Moerman 2012b; Morimoto 2003; Murkin 2009). Intraoperative CDEs were shown to correlate with increased risk of stroke, postoperative cognitive dysfunction (POCD), major organ morbidity or mortality and prolonged length of hospital stay (Monk 2008; Murkin 2007; Olsson 2006; Schön 2009; Slater 2009; Yao 2004). The hospital mortality of stroke patients after cardiac surgery is much higher than that of patients without stroke (19% versus 4%) (Salazar 2001). Moreover, cerebral oxygen desaturations may be related to postoperative neurological dysfunction and worse neurobehavioural outcome (Aguirre 2014; Colak 2012). In paediatric patients, postoperative neurodevelopmental abnormalities were associated with perioperative CDEs in paediatric biventricular repair operations (Kussman 2010). Intervention for CDEs was shown to result in a decreased incidence of postoperative cognitive decline, less major organ morbidity or mortality and shortened intensive care unit and hospital stay following coronary artery bypass grafting (Murkin 2007; Slater 2009).

Description of the intervention

Successful intervention for perioperative cerebral ischaemia and hypoxia relies on early diagnosis (Ng 2011). Various modalities, including electroencephalogram (EEG), somatosensory evoked potential (SSEP), motor evoked potential (MEP), transcranial doppler (TCD), bispectral index (BIS), jugular bulb venous blood haemoglobin saturation ($SjvO_2$) and biomarkers, have been adopted for this purpose with varying limitations (Andropoulos 2004; Guo 2011; Inoue 2013; Sanchez-Pena 2012; Williams 1994). Cerebral near-infrared spectroscopy (NIRS) is increasingly used in clinical settings to monitor brain oxygenation.

Near-infrared light (700 to 1000 nanometres) can penetrate through the superficial layers of the head, including the scalp and the skull, and can illuminate the cerebral tissue. The work by Jöbsis pioneered the use of NIRS to monitor $rScO_2$ (Jöbsis 1977). $rScO_2$ is the percentage of oxy-haemoglobin over the sum of oxy- and deoxy-haemoglobin in pooled arterial, capillary and venous blood in the illuminated brain region. $rScO_2$ is essentially determined by cerebral metabolic rate of oxygen ($CMRO_2$) (demand) and oxygen delivery to the brain (supply). It can be altered by a change in volume percentage of cerebral arterial and/or venous blood (Kurth 1999; Watzman 2000; Yoshitani 2005). CDE treatment aims to augment cerebral blood flow and arterial blood oxygen content, as well as to reduce cerebral oxygen consumption (Subramanian 2016). There is variation among the intervention protocols adopted by previous studies (Ballard 2012; Goldman 2004; Murkin 2007). This may be due to differences in local practice style, types of surgery and patients' individual conditions. Cerebral NIRS has been used in cardiac and major vascular surgeries in both adults and children and in various non-cardiac surgeries, but mainly in adults (Hirsch 2009).

Current cerebral oximetries used in the clinical setting are based on continuous-wave technology; newer technologies such as time-domain and frequency-domain NIRS are based on the transition from bench to bedside (Ferrari 2012; Watzman 2000). Although algorithm differences exist among continuous-wave devices used in patients, the fundamental principle is the same as that previously reviewed (Ferrari 2012; McCormick 1991; Murkin 2009). So far, five NIRS-based cerebral oximetries have been approved for patient use by the US Food and Drug Administration (FDA), including CerOx (Ornim, Inc., Dedham, Massachusetts, USA), EQUANOX 7600 and 8004CA (Nonin Medical, Inc., Plymouth, Minnesota, USA), FORE-SIGHT (CAS Medical Systems, Branford, Connecticut, USA) and INVOS (Somanetics Corporation, Troy, Michigan, USA). Examples of non-approved devices include NIMO (Nirox s.r.l., Brescia, Italy), NIRO-200NX and TRS-20 (Niro, Hamamatsu, Japan), Oxymon-II A and PortaLite (Artinis, Elst, Netherlands) and OxiplexTS (ISS, Champaign, Illinois, USA) (Ferrari 2012; Zheng 2013).

How the intervention might work

Clinical studies suggest that NIRS-based cerebral oximetry can reliably detect perioperative CDEs, especially in cardiac surgery (Bhatia 2007; Casati 2005; Egawa 2009; Greenberg 2013; Kussman 2010; Lovell 1999; Moreno 2013; Murkin 2007; Slater 2009). Various protocols aimed at CDE correction have been proposed (Scheeren 2012; Taillefer 2005). The refined algorithm has improved the accuracy of cerebral NIRS (Fischer 2008). However, bias in NIRS-measured $rScO_2$ still exists both between individuals and between different devices, likely because of differences in skin colour and gender and in the volume percentage of arterial and venous blood in the monitored brain region (Bickler 2013).

NIRS-measured $rScO_2$ reflects the balance between cerebral oxygen consumption and supply. Differential diagnosis is needed when the cause of a change in $rScO_2$ is deciphered. Denault et al proposed an intervention algorithm for CDEs that involves increasing cerebral oxygen supply and/or decreasing consumption (Denault 2007). This algorithmic strategy has been tested in a prospective study that successfully used it to reverse decreased $rScO_2$ in high-risk cardiac surgery patients in both the operating room and the intensive care unit (Deschamps 2013). The effort involved in applying cerebral NIRS in the perioperative setting is encouraged by the fact that NIRS is non-invasive, continuous and applicable at the patient's bedside. This new, non-invasive technique may act as a warning sign of cerebral ischaemia and hypoxia (Tsai 2016). However, whether a perioperative monitor can facilitate decision-making in the implementation of treatment strategies to reverse cerebral desaturation, reduce adverse neurological events and improve overall outcomes in a cost-effective manner needs to be rigorously tested by randomized controlled trials (RCTs).

Why it is important to do this review

One of the fundamental goals of perioperative management is to avoid tissue ischaemia and hypoxia. This is especially true for vital organs such as the brain. It has been shown that low $rScO_2$ is associated with neurological injury under various cardiopulmonary bypass conditions in piglets (Anttila 2005; Hagino 2005). Several clinical studies in adults have also demonstrated the association between intraoperative CDEs and adverse neurological outcomes, POCD, major organ morbidity or mortality and prolonged length of hospital stay (Monk 2008; Murkin 2007; Slater 2009; Vohra 2009; Yao 2004). In paediatric patients, cerebral NIRS seems to correlate with vital parameters and enhance the prediction of neurodevelopmental outcomes after cardiac surgery (Kussman 2010; Menke 2014; Sood 2013). Cerebral NIRS is also increasingly being applied in the cardiac ICU for perioperative brain oxygenation monitoring (Ghanayem 2016). In addition, real-time brain oxygenation monitoring with cerebral NIRS may be beneficial for detecting ischaemic events during cerebrovascular procedures and in the neurosurgical ICU (Calderon-Arnulphi 2007; Grinspan 2014; Mazzeo 2012; Obrig 2014). However, evidence to support the predictive value of cerebral NIRS for adverse neurological outcome is lacking and a very limited number of RCTs have tested the beneficial effect of cerebral NIRS on outcomes in adult cardiac patients (Zheng 2013). Currently, the hypoxic threshold based on cerebral NIRS monitoring for intervention is poorly defined (Denault 2007; Fischer 2011; Murkin 2007; Orihashi 2004). In non-cardiac surgery, especially routine surgery under general anaesthesia, the role of cerebral NIRS is undefined (Ghosh 2012). Without well-defined outcomes from the use of NIRS and associated implemented treatment strategies, it is difficult to support the use of NIRS in the clinical setting (Hirsch 2010). In addition, cost-effectiveness analysis needs to be done to support the benefits of cerebral NIRS. Therefore, an up-to-date review of the use of cerebral NIRS in the perioperative setting based on RCTs could be pivotal, not only in defining the areas where clarification or rigorous evidence is needed but also in guiding its application in the clinical setting.

OBJECTIVES

To assess the effects of perioperative cerebral NIRS monitoring and corresponding treatment strategies in adults and children, compared with no cerebral oxygenation monitoring or cerebral oxygenation monitoring based on non-NIRS technologies, on the detection of CDEs, neurological outcomes, non-neurological outcomes and socioeconomic impact (including cost of hospitalization and length of hospital stay).

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs dealing with the use of cerebral NIRS in the perioperative setting (during the operation and within 72 hours after the operation), including the operating room (OR), the postanaesthesia care unit (PACU) and the intensive care unit (ICU). We included all appropriate studies without regard for publication status or language used. We excluded non-randomized studies such as cohort studies, which are susceptible to bias.

Types of participants

We included adult participants (aged 18 years or older) and paediatric participants (aged younger than 18 years, excluding neonates) of both genders undergoing any types of surgery under general anaesthesia. We also included operations sometimes undertaken under local anaesthesia, such as carotid artery stenting and carotid endarterectomy. We excluded neonates because there is a review published by the Cochrane Neonatal Group (Hyttel-Sorensen 2017).

Types of interventions

The intervention group included all surgical participants who received cerebral NIRS monitoring and interventions to correct CDEs in the perioperative setting. So far, five NIRS-based cerebral oximetries have been approved by the US Food and Drug Administration (FDA). We documented the type of device used in each study and carried out subgroup analyses.

The control group included surgical participants monitored by conventional monitors (e.g. heart rate, mean arterial pressure) or other kinds of monitors such as electroencephalogram (EEG), transcranial doppler (TCD), bispectral index (BIS), jugular bulb oximetry, evoked potentials, cerebral tissue oxygen partial pressure (PbO_2), etc. The control group received no monitoring by cerebral NIRS or blinded monitoring where the $rScO_2$ readout was concealed from the anaesthesiologist.

Types of outcome measures

Primary outcomes

1. Postoperative stroke or other neurological injury, including adverse neurodevelopmental outcomes (within 24 hours postoperatively up to discharge or the end of follow-up). The diagnosis was based on new-onset neurological deficits, and findings were based on the neurological examination or neuroradiological evidence including computed tomography (CT), magnetic resonance imaging (MRI) or neuroangiography. Neurological deficits included abnormalities of sensory, motor, balance, speech, vision or autonomic nervous system functions.
2. Postoperative delirium (POD) or POCD (within 24 hours postoperatively up to discharge). The diagnosis of POD or POCD was based on the criteria adopted by the authors in each included study.
3. Intraoperative mortality or postoperative mortality (at 24 hours, 30 days and one year after surgery).

Secondary outcomes

1. The occurrence of abnormal $rScO_2$ during or after surgery: the definition was attributed to the varying NIRS devices and differing physical and medical conditions of the participants. We used the criteria adopted by each included study.
2. Any major non-neurological complications that occurred during the intraoperative or postoperative period.
   a. Respiratory insufficiency caused by pneumonia (fever, leukocytosis, chest x-ray or positive sputum culture), atelectasis (diagnosed based on chest x-ray), pulmonary emboli (sudden death confirmed by positive radiological findings) or pneumothorax (chest x-ray).
   b. Cardiovascular complications, including myocardial infarction (electrocardiogram (ECG) changes confirmed by

abnormal myocardial enzymes), cardiac failure (clinical signs and symptoms or positive radiological findings), malignant arrhythmia (ECG changes) or cardiac arrest (ECG changes).

c. Hepatic or renal insufficiency (clinical manifestations and laboratory evidence).

3. ICU length of stay.
4. Hospital length of stay.
5. Cost of hospitalization.
6. Adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 12), Embase (1974 to 20 December 2016) and MEDLINE (PubMed) (1975 to 20 December 2016), with no language restrictions. YY performed the search on 20 December 2016. We performed a further search in November 2017. We have added the results for the latter search to Studies awaiting classification and we will incorporate them into the review at the next update.

We used search strategies to maximize sensitivity by following Section 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* to search for RCTs in Embase and PubMed (Higgins 2011). We searched CENTRAL, Embase and PubMed using the search terms described in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources

We scanned the reference lists of all eligible articles and reviews to identify further RCTs.

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform on 20 December 2016, including ClinicalTrials.gov, the *meta*Register of Controlled Trials and other national trial registries, for ongoing studies. We contacted relevant specialists in this field to identify unpublished research and ongoing trials on 24 March 2016.

We imposed no language or region restrictions.

Data collection and analysis

Selection of studies

Two review authors (YY and KZ) independently screened the results of the searches and recorded separately the reasons for inclusion or exclusion. We excluded duplicate records. We excluded studies in animal models. We resolved disagreements on study selection between review authors via discussion. If needed, we consulted with a third review author (RH or LM) to resolve any disagreements. If further information was required, YY contacted the corresponding author of the study.

Data extraction and management

We used a pre-designed form to record the data obtained from included studies (Appendix 4). Two review authors (YY and KZ) independently extracted data using a paper data extraction form (Appendix 4). We resolved disagreements via discussion. If we were unable to reach a consensus, we consulted a third review author (RH or LM). If further information was needed, YY contacted the corresponding author of the study.

Assessment of risk of bias in included studies

Two review authors (YY and KZ) independently assessed the risk of bias of all included studies. We tried to resolve disagreements by discussion and, if a consensus could not be reached, a third review author (LZ) was consulted.

We assessed the risk of bias of the included studies using the 'Risk of bias' tool that is described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A copy of the assessment form that we adopted can be found in Appendix 4.

We evaluated each study according to the following domains: selection bias, performance bias and attrition bias, including randomization and allocation concealment, blinding of participants, blinding of outcome assessment, missing data, selective reporting and any other bias. We assessed blinding separately for subjective (e.g. POCD) and objective (e.g. mortality) outcome measures. Objective outcome measures were less likely to be influenced by the knowledge of research personnel.

We rated a study as having 'low risk of bias' if all of the domains were assessed as adequate. We rated a study as having 'high risk of bias' if one or more of the domains were identified as inadequate or unclear. We performed sensitivity analyses to assess the influence of the exclusion of 'high risk of bias' studies on the results of the meta-analysis.

We presented a 'Risk of bias' table for each included study using the classification of 'low', 'high' or 'unclear' risk of bias. We also completed a 'Risk of bias' summary figure for each outcome to present a detailed description of all judgements made for all eligible studies in the review.

Measures of treatment effect

We analysed data using the Review Manager software (RevMan 5.3).

Dichotomous data

For dichotomous data, for example, whether cerebral NIRS was associated with postoperative neurological injury during the perioperative period, as well as reduction in mortality at 24 hours, 30 days and one year, we used a random-effects model for analysis to estimate the overall risk ratio (RR) with the 95% confidence interval (CI).

Continuous data

For continuous data, such as length of ICU or hospital stay in days, we used mean differences (MDs) as summary statistics in the meta-analysis.

Time-to-event data

There were no time-to-event data reported in the included studies, therefore we did not perform survival analysis.

Unit of analysis issues

We included RCTs with a parallel-group design. However, we did not find any cluster-randomized controlled trials (cluster-RCTs).

Dealing with missing data

We (YY) contacted the original investigators to request any missing data required for meta-analysis. We assumed the data to be

missing at random and we analysed only the available data, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed sensitivity analyses to assess how sensitive the results were to reasonable changes in our assumptions. In the Discussion section, we addressed the potential impact of missing data on the conclusions of the review.

Assessment of heterogeneity

We appraised the heterogeneity of the included studies based on both clinical diversity (e.g. type of surgery, type of anaesthesia, participants' comorbidities) and methodological diversity (risk of bias assessment). We performed subgroup analysis and sensitivity analysis to address clinical heterogeneity, including visual inspection of the forest plots and determining the I^2statistic (Higgins 2011). We considered an I^2 statistic exceeding 50% to show high levels of heterogeneity, mandating further analysis.

Assessment of reporting biases

Although we included 15 studies in this review, fewer than 10 were involved in the meta-analysis for each outcome. As a result, we did not create a funnel plot to qualitatively assess publication or reporting bias.

Data synthesis

If the included studies did not have excessive clinical or statistical heterogeneity, we used the Review Manager software to combine the data on population, interventions and outcomes and performed a meta-analysis to generate a quantitative summary. As we expected clinical and methodological heterogeneity between studies, we analysed the data with a random-effects model. If suitable numerical data were insufficient for a meta-analysis, we carried out a narrative analysis for each study and summarized all of the qualified data.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses as follows, including subgroups of participants and interventions.

Subgroups of participants

Subgroup analysis according to type of surgery

1. Participants undergoing neurosurgery.
2. Participants undergoing cardiac or great vessel surgery with/without bypass.
3. Participants undergoing carotid endarterectomy.
4. Participants undergoing other surgery.

In this review, we did not perform subgroup analysis according to age of participants because none of the included studies considered a paediatric population.

Subgroups of interventions

1. Perioperative cerebral NIRS monitoring versus no cerebral oxygenation monitoring.
2. Perioperative cerebral NIRS monitoring versus other kinds of cerebral oxygenation monitoring.

Subgroup analysis according to documentation of device types

1. INVOS (Somanetics Corporation, Troy, Michigan, USA).
2. CerOx (Ornim, Inc., Dedham, Massachusetts, USA).
3. EQUANOX 7600 (Nonin Medical, Inc., Plymouth, Minnesota, USA).
4. EQUANOX 8004CA (Nonin Medical, Inc., Plymouth, Minnesota, USA).
5. FORE-SIGHT (CAS Medical Systems, Branford, Connecticut, USA).

Sensitivity analysis

We carried out sensitivity analyses to assess the effects of study risk of bias by excluding each study sequentially and we excluded studies at high risk of bias, which had inadequate allocation of concealment.

'Summary of findings' table and GRADE

We used the principles of the GRADE system to assess the quality of the body of evidence associated with the specific outcomes (rate of postoperative stroke or other neurological injury, POD, POCD or mortality at 24 hours, 30 days and one year, and adverse events) and we constructed a 'Summary of findings' table using the GRADEpro software (Guyatt 2008). We generated a 'Summary of findings' table for 'Active cerebral oxygenation monitoring compared to blinded cerebral oxygenation monitoring'.

The GRADE approach evaluates the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considered risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

Description of studies

Please see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies for further details.

Results of the search

We identified 3145 potential references from the electronic search and one additional reference through handsearching on 20 December 2016. Two review authors (YY and KZ) independently reviewed the results and were able to exclude 2234 citations through title and abstract screening. We screened 65 full-text articles for further assessment of which 15 were subsequently included in this review (Ballard 2012; Casati 2005; Colak 2015; Cowie 2014; Deschamps 2013; Deschamps 2016; Harilall 2014; Kara 2015; Lau 2012; Mohandas 2013; Murkin 2007; Slater 2009; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011). Moreover, there are nine studies awaiting classification, comprising one protocol for a RCT and eight conference abstracts (Aguirre 2016; Baker 2006; Ellis 2015; Gauge 2014; Girgin 2012; Iglesias 2003; Sahan 2014; Trinh 2016; Verborgh 2009). Two study reports (Lei 2017; Rogers 2017) and one conference abstract (Hosang 2017) from an updated search in November 2017 have been added to 'Studies awaiting classification' (Characteristics of studies awaiting classification). There are eight ongoing trials currently without available data from the investigators (Bal 2016; Djaiani 2012; Fischer 2009; Fominskiy 2014; Grocott 2013; Shi 2013; Teurnier 2011;Trinh 2012). The

ongoing trials were retrieved from other resources, such as the ClinicalTrials.gov.

Please refer to Figure 1 and Figure 2.

Figure 1. Study flow diagram.

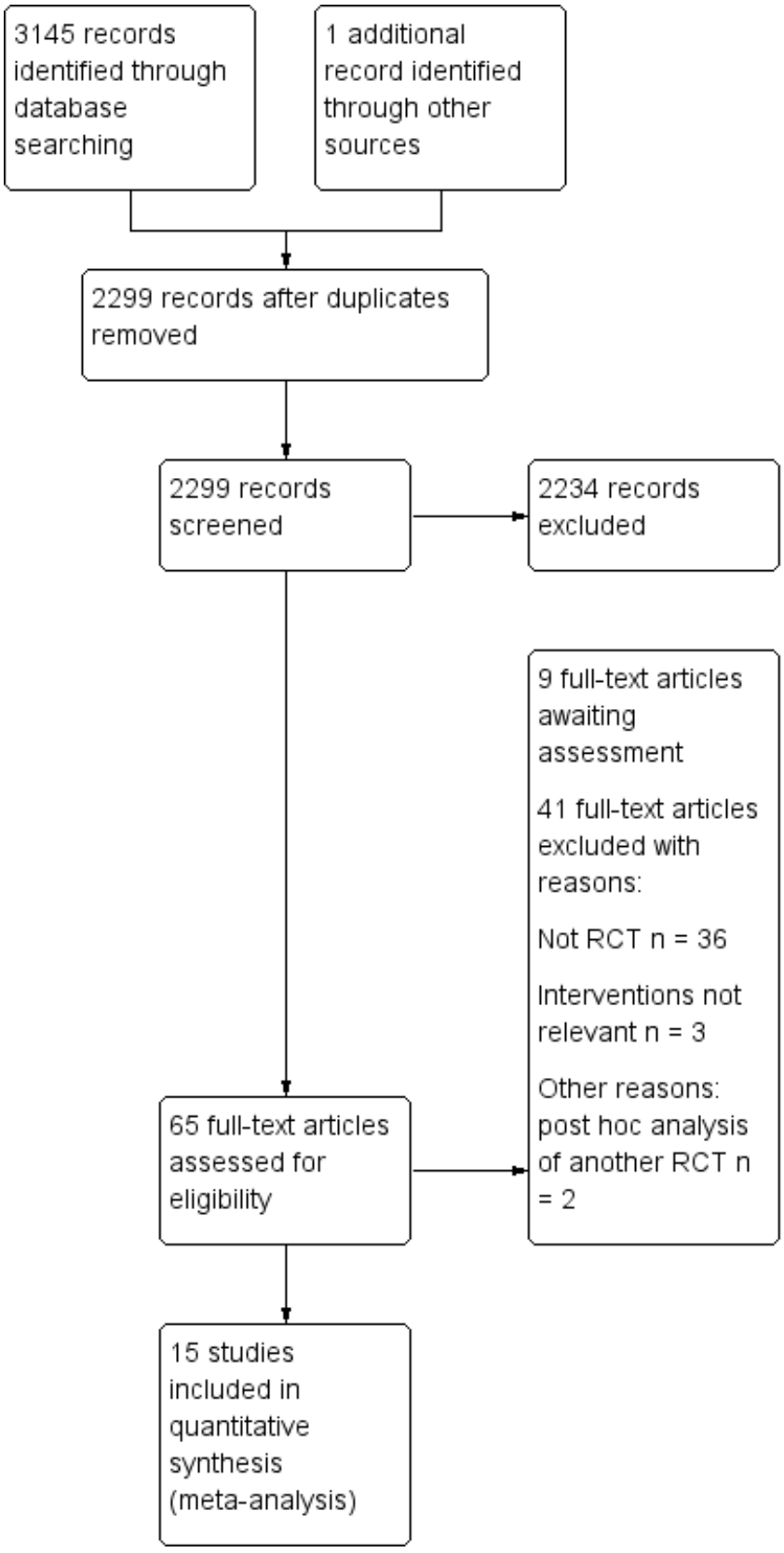
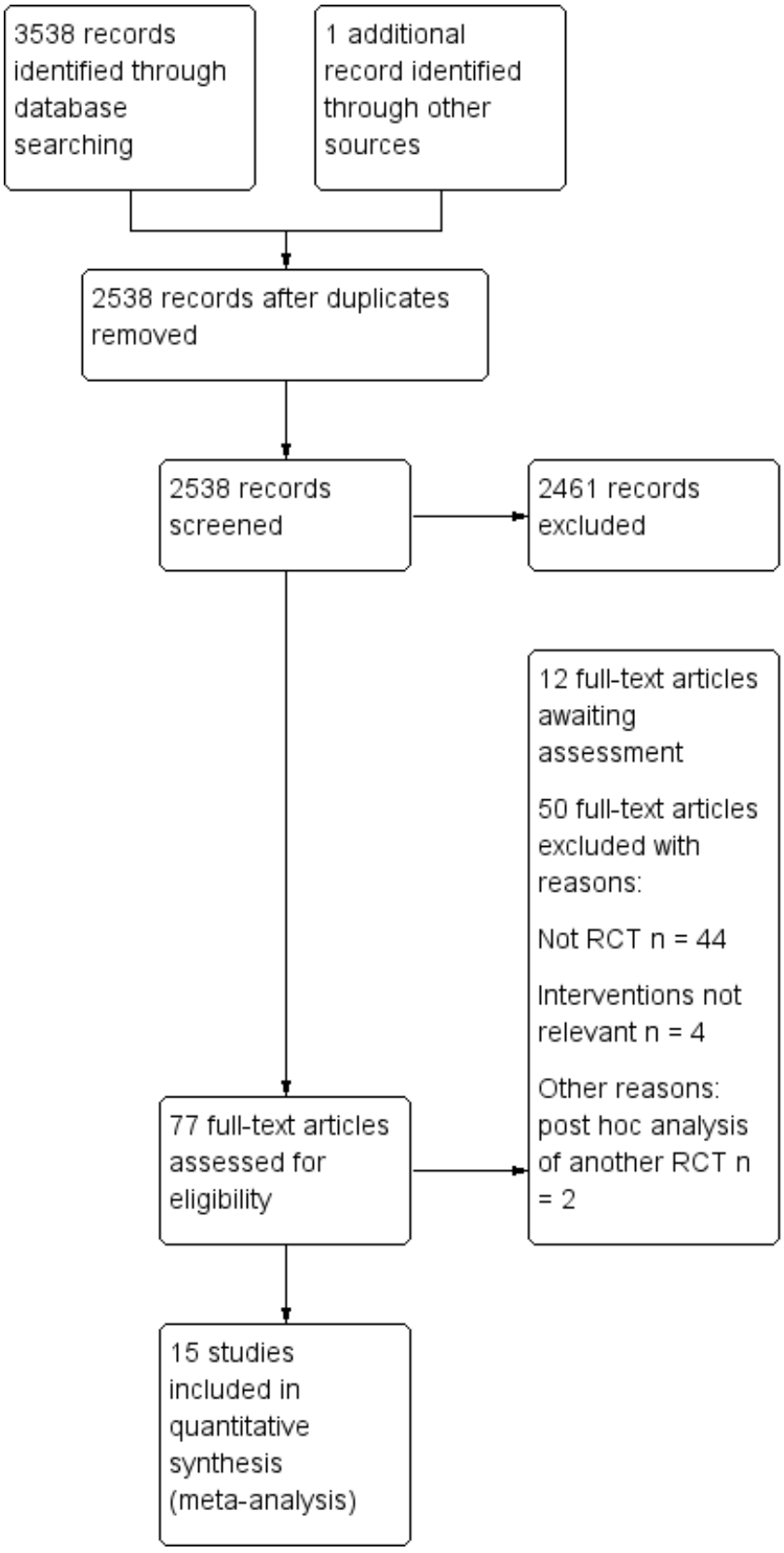


Figure 2. Study flow diagram-top up search on November 2017.



Included studies

Methods

All the included studies employed a parallel-group, randomized study design. No studies used a quasi- or cluster-randomized design.

Participants

A total of 1822 adults participated in 15 studies. The total sample size ranged from 25 to 253. None of the 15 included studies considered the paediatric population.

Settings

Four of the 15 included studies were conducted in the abdominal or orthopaedic (lumbar spine, or knee and hip replacement surgery) setting (Ballard 2012; Casati 2005; Cowie 2014; Trafidlo 2015), one study in the carotid endarterectomy setting (Zogogiannis 2011), and the remaining 10 studies in the aortic or cardiac surgery setting (Colak 2015; Deschamps 2013; Deschamps 2016; Harilall 2014; Kara 2015; Lau 2012; Mohandas 2013; Murkin 2007; Slater 2009; Vretzakis 2013). One study was conducted under local anaesthesia (Zogogiannis 2011). Three studies were conducted in Canada (Deschamps 2013; Deschamps 2016; Murkin 2007), two in the United States (Slater 2009; Vretzakis 2013), one in the United Kingdom (Ballard 2012), one in Croatia (Colak 2015), one in Australia (Cowie 2014), one in South Africa (Harilall 2014), one in Turkey (Kara 2015), one in Poland (Trafidlo 2015) and one in Greece (Zogogiannis 2011). The remaining three studies did not provide detailed information about the country in which they were conducted (Casati 2005; Lau 2012; Mohandas 2013).

Study period

Ballard 2012 recruited participants from March 2007 to January 2009, Colak 2015 from June 2009 to September 2011, Cowie 2014 from February 2012 to September 2012, Deschamps 2016 from April 2012 and October 2013, Kara 2015 from December 2013 to February 2015, Lau 2012 from November 2009 to September 2011, Murkin 2007 from September 2002 to April 2004, Slater 2009 from January 2004 to February 2006, and Zogogiannis 2011 from December 2007 to January 2010. The remaining six studies did not report the exact study period (Casati 2005; Deschamps 2013; Harilall 2014; Mohandas 2013; Trafidlo 2015; Vretzakis 2013).

Interventions

All of the included studies used cerebral NIRS in the perioperative setting. In order to correct CDEs, all surgical participants received cerebral NIRS monitoring in the perioperative setting. The types of device documented included EQUANOX 7600 (Mohandas 2013; Deschamps 2016), FORE-SIGHT (Deschamps 2016) and INVOS (i.e. INVOS Somanetics Cerebral Oximeter (Covidien, USA) or SCIO (i.e. Somanetics Invos Cerebral Oximeter (SICO, Covidien inc, Co, USA)) in the remaining 14 studies (Ballard 2012; Casati 2005; Colak 2015; Cowie 2014; Deschamps 2013; Deschamps 2016; Harilall 2014; Kara 2015; Lau 2012; Murkin 2007; Slater 2009; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011).

The control group in the following studies either did not receive cerebral oxygenation monitoring (Colak 2015; Kara 2015; Vretzakis 2013; Zogogiannis 2011), or the $rScO_2$ was collected but was concealed from the anaesthesiologist (Ballard 2012; Casati 2005; Cowie 2014; Deschamps 2013; Deschamps 2016; Harilall 2014; Lau 2012; Mohandas 2013; Murkin 2007; Slater 2009). One study described the comparison as INVOS monitoring versus no monitoring, but no further detail about the control group was provided (Trafidlo 2015). In Zogogiannis 2011, cerebral oximetry values were recorded in group B but anaesthesia management was not based on the algorithm mentioned in the full text; therefore, we only used the data from group A as the intervention group.

Outcomes

All 15 included studies reported the pre-specified primary and secondary outcomes except for the cost of hospitalization. This current review did not analyse additional outcomes measured in five studies (33%), which were not mentioned in our protocol, such as rate of ICU stay, rate of hospitalization and management of hypotension without cerebral oximetry reasons (Cowie 2014; Deschamps 2013; Mohandas 2013; Murkin 2007; Vretzakis 2013).

Two studies (13%) considered loss to follow-up in the sensitivity analysis (Ballard 2012; Lau 2012). However, no data were obtained through contacting the original investigators (Characteristics of included studies). In terms of funding sources, four studies (27%) may have been potentially influenced by the financial or commercial interests of the investigators (Ballard 2012; Cowie 2014; Deschamps 2016; Murkin 2007).

Excluded studies

We excluded three studies from this review for the reasons listed in the Characteristics of excluded studies table.

Kussman 2009 was a cohort study, which was part of a RCT comparing early postoperative and neurodevelopmental outcomes after haemodilution to a haematocrit of 25% versus 35% during infant heart surgery.

Kussman 2010 was a secondary analysis of data arising from a RCT of haemodilution to a haematocrit of 25% versus 35% during cardiopulmonary bypass in infants. The authors evaluated the correlation between intraoperative cerebral oxygen saturation and postoperative neurological outcomes at the age of one year.

Murkin 2011 was a post hoc analysis of a subset of participants in Murkin 2007 and focused on participants with a preoperative diagnosis of diabetes mellitus. The remaining excluded studies were observational studies and not RCTs.

Studies awaiting classification

Nine studies are awaiting classification (Characteristics of studies awaiting classification). One study was the protocol for a RCT that met our inclusion criteria (Ellis 2015). The remaining eight studies were conference abstracts (Aguirre 2016; Baker 2006; Gauge 2014; Girgin 2012; Iglesias 2003; Sahan 2014; Trinh 2016; Verborgh 2009). We tried to contact the relevant research group through their institutions for further information about these studies (Characteristics of studies awaiting classification). Two RCTs meeting the inclusion criteria (Lei 2017; Rogers 2017) and a conference abstract (Hosang 2017) from an updated search in November 2017 have also been added to 'Studies awaiting classification' (Characteristics of studies awaiting classification).

Ongoing studies

By searching multiple clinical trials registry platforms, we identified eight ongoing studies (Characteristics of ongoing studies). Five of the ongoing studies were conducted in a cardiac surgery setting (Djaiani 2012; Fischer 2009; Fominskiy 2014; Grocott 2013; Trinh 2012), two studies in an oesophagectomy or orthopaedic setting (Bal 2016; Shi 2013), and one study in a carotid endarterectomy setting (Teurnier 2011). Four of these studies were recruiting participants (Fischer 2009; Fominskiy 2014; Grocott 2013; Trinh 2012), one study was completed (Bal 2016), one study was terminated (Teurnier 2011), and the remaining studies were pending (Djaiani 2012; Shi 2013).

Risk of bias in included studies

See also the 'Risk of bias' tables in Characteristics of included studies and Figure 3 and Figure 4.

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

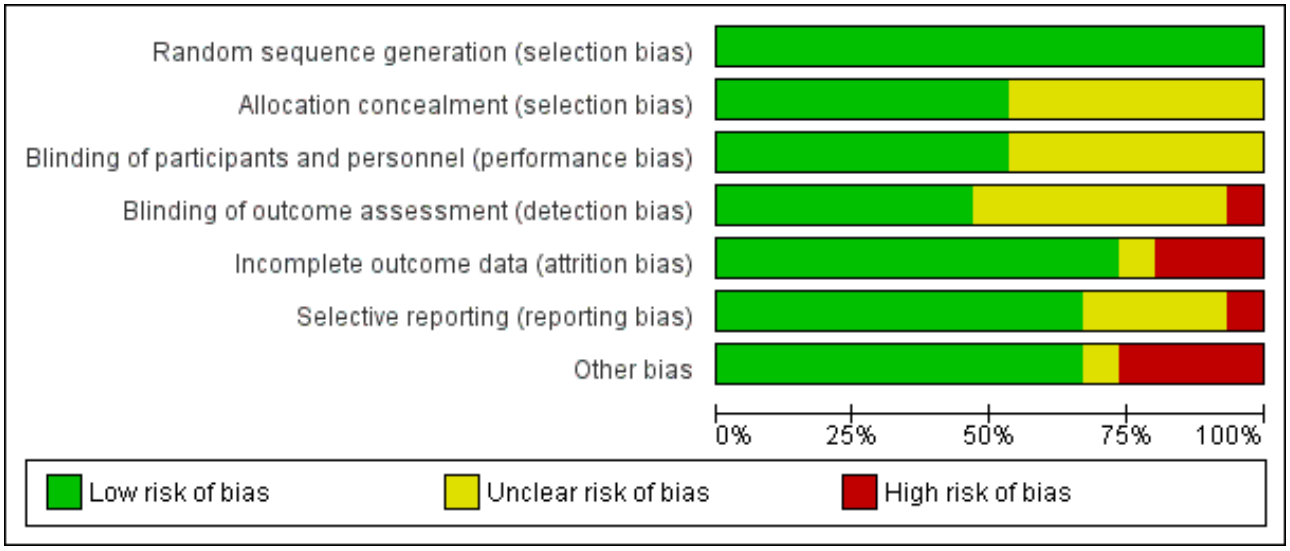
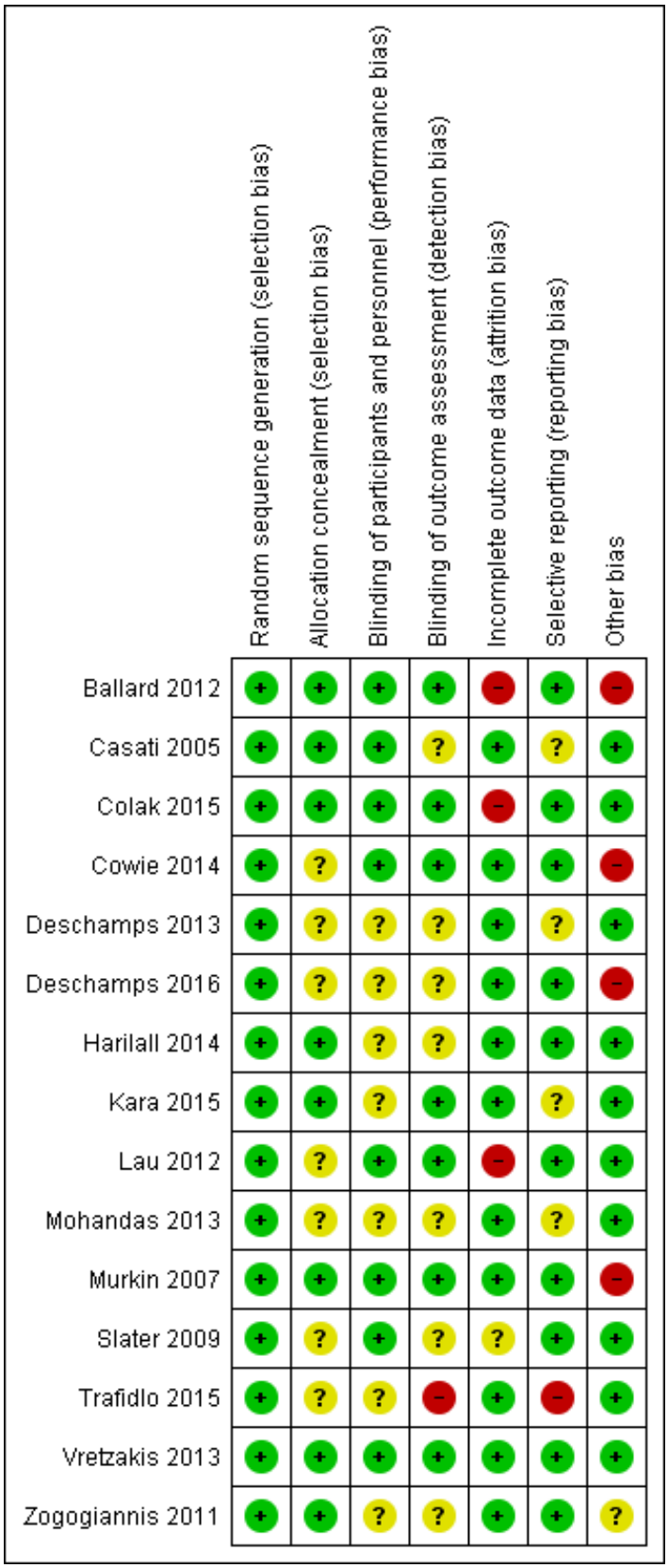


Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All included studies were RCTs and random sequence generation was employed in all of them. Seven studies, however, did not provide adequate details of their randomization methods and simply stated that they were randomized (Deschamps 2013; Kara 2015; Lau 2012; Mohandas 2013; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011). As we accepted the trialist's reporting as true and accurate, we rated all 15 studies as being at a low risk of bias. Random sequence generation was adequately described in eight studies (53%) using the statistical program package R, a computer-generated sequence of numbers or a random numbers table (Ballard 2012; Casati 2005; Colak 2015; Cowie 2014; Deschamps 2016; Harilall 2014; Murkin 2007; Slater 2009). The common method used in seven studies to conceal allocation was sequentially numbered, opaque, sealed envelopes (Ballard 2012; Casati 2005; Colak 2015; Harilall 2014; Murkin 2007; Vretzakis 2013; Zogogiannis 2011). One study described the randomization list being concealed until the study was concluded; in this case we accepted the authors' reporting as true and accurate and rated this study as low risk of bias (Kara 2015). The remaining seven studies did not describe the method of concealment and we rated them as having unclear risk of bias (Cowie 2014; Deschamps 2013; Deschamps 2016; Lau 2012; Mohandas 2013; Slater 2009; Trafidlo 2015).

Blinding

Blinding of participants and key study personnel was ensured in eight studies (53%) and we rated them as at low risk of bias (Ballard 2012; Casati 2005; Colak 2015; Cowie 2014; Lau 2012; Murkin 2007; Slater 2009; Vretzakis 2013). There was insufficient information about blinding of participants and personnel in the remaining seven studies (Deschamps 2013; Deschamps 2016; Harilall 2014; Kara 2015; Mohandas 2013; Trafidlo 2015; Zogogiannis 2011). Hence, we rated them as having unclear risk of bias.

Blinding of outcome assessors was ensured in seven studies (47%) and consequently we rated these as low risk of bias (Ballard 2012; Colak 2015; Cowie 2014; Kara 2015; Lau 2012; Murkin 2007; Vretzakis 2013). In Casati 2005, some research personnel may also have been the outcome assessors, hence we assessed this study as having an unclear risk of bias. However, Trafidlo 2015 stated that the observers were not blinded and thus we rated it as having a high risk of bias. There was insufficient information about blinding of outcome assessment in the remaining six studies (40%) and we thus rated these as having an unclear risk of bias (Deschamps 2013; Deschamps 2016; Harilall 2014; Mohandas 2013; Slater 2009; Zogogiannis 2011).

Incomplete outcome data

In 11 out of 15 included studies (73%), all randomized participants were analysed for all expected outcomes and we consequently awarded them a low risk of bias (Casati 2005; Cowie 2014; Deschamps 2013; Deschamps 2016; Harilall 2014; Kara 2015; Mohandas 2013; Murkin 2007; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011). In Casati 2005, after randomization, seven participants were excluded from the treatment group while two participants were excluded from the control group for the following reasons: insertion of an epidural catheter, cancellation, technical failure and death due to surgical complications. The reasons for the missing data were unlikely to influence the outcomes. In Murkin 2007, rSO_2 data were lost in six participants because of technical failure (3% of sample size). In Zogogiannis 2011, 2 out of the 253 participants (0.8% of sample size) died because of postoperative cardiovascular events. In two studies, the proportion of missing outcomes compared with observed events was not likely to induce clinically relevant bias in the intervention effect estimate (Murkin 2007; Zogogiannis 2011). However, in Ballard 2012, two participants were excluded from the analysis due to delirium, which was an unacceptable reason for exclusion and the levels of missing data were high (at one week after surgery: 35.3% in the intervention group and 23.7% in the control group, respectively; at 12 weeks: 20.6% and 10.5%, respectively; at 52 weeks: 17.7% and 15.8%, respectively). Hence, we rated it as high risk of bias. In Slater 2009, the authors did not provide information about withdrawal or loss to follow-up but reported that 16% of participants had no neurocognitive testing at three months. In Colak 2015, out of 200 participants, six in the intervention group and four in the control group were excluded from the analysis because the participants did not receive the allocated intervention. We regarded the reason for excluding participants as unacceptable and thus we rated it as high risk of bias. Lau 2012 was at a high risk of bias due to a significant amount of incomplete outcome data (2 out of 12 in the intervention group and 3 out of 13 in the control group were dropouts).

Selective reporting

All expected outcomes were reported in nine of the included studies (60%), which we rated as low risk of bias (Colak 2015; Cowie 2014; Deschamps 2016; Harilall 2014; Lau 2012; Murkin 2007; Slater 2009; Vretzakis 2013; Zogogiannis 2011). In Ballard 2012, the authors did not present the "Trail Making" data at one week postoperatively or the S100B data in the intervention group and the control group. However, this is unlikely to have had an important influence on the estimate of the effects of the prespecified outcomes of this review, hence we rated it as low risk of bias. Mohandas 2013 had an unclear risk of bias because one secondary outcome (the number of participants experiencing desaturation) was not reported. We rated Kara 2015 as unclear risk of bias because one secondary outcome (intraoperative rSO_2 parameters) was not reported. The predefined outcomes were not clarified in the methods section in the other two studies, hence we rated them as unclear risk of bias, as we did not have sufficient information to make a firm judgement (Casati 2005; Deschamps 2013). We also rated Trafidlo 2015 as high risk of bias as although all prespecified outcomes were reported, the numbers of participants in the Digit Span Test (DST) and the N-back Test (NBT) were different from the randomized number.

Other potential sources of bias

Four of the included studies (27%) appeared to have other potential sources of bias. In Ballard 2012, two of the authors may have had financial or commercial conflicts of interest, hence we rated this domain as high risk of bias. Commercial funding was also apparent in Cowie 2014, Murkin 2007 and Deschamps 2016, therefore we rated them as high risk of bias. Cowie 2014 was supported by an equipment grant (device loan and sensors) from Covidien USA (Mansfield, MA) and also by an Australian and New Zealand College of Anaesthetists pilot trial grant. There was no obvious commercial involvement in the other studies.

Effects of interventions

See: **Summary of findings for the main comparison** Active cerebral oxygenation monitoring compared to blinded cerebral oxygenation monitoring for perioperative monitoring of brain oxygenation in children and adults

1. Comparison 1: Active cerebral oxygenation monitoring versus blinded cerebral oxygenation monitoring

Primary outcomes: postoperative stroke or other neurological injury

1.1 Postoperative stroke or other neurological injury

Neurological injury was investigated by two relevant studies (n = 312) (Casati 2005; Colak 2015). Neither study showed a significant difference between interventions. The direction of effect favoured different interventions in these studies, hence when we tried to pool the results we observed a high level of heterogeneity (I^2 = 72%). This was probably due to the clinical diversity of participants. Casati 2005 involved participants undergoing major abdominal, nonvascular surgery under general anaesthesia (with an expected duration of more than two hours). In contrast, Colak 2015 included participants undergoing on-pump coronary artery bypass grafting (CABG) surgery with the use of cardiopulmonary bypass. Consequently, we presented the results of each study separately without meta-analysis (Casati 2005 n = 126, fixed-effect model, risk ratio (RR) 0.13, 95% confidence interval (CI) 0.01 to 2.37; Colak 2015 n = 195, fixed-effect model, RR 4.09, 95% CI 0.47 to 35.88) (Table 1). We downgraded this outcome to low quality due to risk of bias and inconsistency (Summary of findings for the main comparison).

The estimated effect on stroke based on data from Cowie 2014 and Murkin 2007 was similar between interventions (n = 240, fixed-effect model, RR 0.25, 95% CI 0.03 to 2.20) (Table 1). We downgraded this outcome to low quality due to risk of bias (commercial funding) and imprecision (small sample size) (Summary of findings for the main comparison).

1.2 Postoperative stroke or other neurological injury: mini-mental state examination (MMSE) (endpoint or change score)

Using the MMSE score (maximum score = 30), Ballard 2012, Lau 2012 and Mohandas 2013 measured postoperative stroke or other neurological injury at one, 12 and 52 weeks. Pooled analysis showed that at every measured time point the active cerebral oxygenation monitoring group had a higher mean MMSE score than the blinded monitoring group (2 studies with 151 participants, random-effects model, mean difference (MD) 2.72, 95% CI 1.42 to 4.03, at one week; 3 studies with 179 participants, random-effects model, MD 1.11, 95% CI 0.15 to 2.07, at 12 weeks; and one study with 60 participants, MD 1.63 95% CI 0.7 to 2.56 at 52 weeks) (Analysis 1.1).

1.3 Postoperative stroke or other neurological injury: a simplified antisaccadic eye movement test (ASEM) (endpoint score)

Only Mohandas 2013 (n = 100) observed stroke or neurological injury using the ASEM score and reported a significant difference favouring active cerebral oxygenation monitoring at both one and 12 weeks (MD 2.42, 95% CI 0.98 to 3.86; MD 1.99, 95% CI 0.78 to 3.20, respectively) (Table 1).

1.4 Postoperative stroke or other neurological injury: S100B

For this outcome, Harilall 2014 tested the serum 100B level to indicate postoperative neurological injury, which provided the median and interquartile range (IQR) of the endpoint and change data (n = 40). The blinded monitoring group demonstrated a higher level of S100B at endpoint (median 77.7, IQR 71.4 to 87.6 in the active monitoring group; 176.8, 160.8 to 199.5 in the blinded monitoring group) and change value (37.3, 33.1 to 42.7 in the active monitoring group; 139.3, 123.8 to 159.0 in the blinded monitoring group) than the active monitoring group.

1.5 Postoperative stroke or other neurological injury: vigilance reaction time (change score)

Only Ballard 2012 (n = 61) provided data for the vigilance reaction time at one, 12 and 52 weeks. Only the data at 12 and 52 weeks supported the active monitoring group (MD -25.34, 95% CI -41.44 to -9.24 at 12 weeks; MD -25.9, 95% CI -45.39 to -6.41 at 52 weeks) (Table 1), while both groups had a similar change score for vigilance reaction time at one week (MD -21.56, 95% CI -60.85 to 17.73).

1.6 Postoperative stroke or other neurological injury: trail making test (change score)

Ballard 2012 (n = 61) also provided data for the trail making test at 12 and 52 weeks, which indicated a lower level of trail making at 12 weeks (MD -0.7, 95% CI -1.23 to -0.17) but a higher level at 52 weeks (MD 0.59, 95% CI 0.18 to 1.0) (Table 1) in the active cerebral oxygenation monitoring group compared to the blinded monitoring group.

In Ballard 2012, there were potential risks of bias in terms of incomplete outcome data. In Mohandas 2013, there was insufficient information about allocation concealment and blinding; in addition, the number of participants experiencing desaturation was not reported. In Lau 2012, 2 of 12 in the treatment group and 3 of 13 in the control group were dropouts; the MMSE was analysed with nine participants in each group. Furthermore, the sample size was small and the outcome was indirectly measured via a scale. Therefore, we downgraded these outcomes to very low quality due to risk of bias, imprecision and indirectness (Analysis 1.1; Summary of findings for the main comparison; Table 1).

Primary outcomes: postoperative delirium or postoperative cognitive dysfunction

1.7 Postoperative delirium (POD)

Only Colak 2015 provided data for this outcome and the result indicated that there was no significant difference between groups (n = 190, RR 0.63, 95% CI 0.27 to 1.45) (Table 1). We downgraded this outcome to low quality because only 181 participants (90.5%) had a neurocognitive test at seven days after surgery and the sample size was small (Summary of findings for the main comparison).

1.8 Postoperative cognitive dysfunction (POCD) as defined by the original studies

Two studies (n = 126) provided data for this outcome (Ballard 2012; Kara 2015). Kara 2015 reported mild and severe postoperative cognitive function impairment before discharge, but the detailed time point was not described. Since the hospital length of stay was 7.15 ± 1.39 days versus 7.67 ± 1.14 days in the intervention group and control group, respectively, we pooled the data into the analysis of POCD as defined by the original studies - one week. In terms of mild and severe POCD as defined by the original studies up to one week, there was a significant difference between groups (random-effects model, RR 0.53, 95% CI 0.30 to 0.95; RR 0.18, 95% CI 0.03 to 0.92, respectively) (Analysis 1.2). However, there was no significant difference in the incidence of moderate POCD (RR 0.46, 95% CI 0.2 to 1.04) (Analysis 1.2). See Summary of findings for the main comparison. Ballard 2012 also reported the incidence of mild POCD by 12 weeks; a significant difference was demonstrated

between the two groups (RR 0.66 95% CI 0.44 to 0.99) (Table 1). Ballard 2012 also reported the incidence of POCD by 52 weeks. The active monitoring group saw a significant decrease in the incidence of mild and moderate POCD (RR 0.66, 95% CI 0.46 to 0.95; RR 0.30, 95% CI 0.09 to 0.94, respectively) but the incidence of severe POCD by 52 weeks was similar between the two groups (RR 0.30, 95% CI 0.04 to 2.49) (Table 1). In Ballard 2012, the attrition rates at one week postoperatively were 35.3% (intervention group) and 23.7% (control group), respectively; at 12 weeks they were 20.6% and 10.5%, respectively; and at 52 weeks they were 17.7% and 15.8%, respectively. The proportion of missing outcomes compared with the observed events could possibly induce clinically relevant bias in the intervention effect estimate. As a result, we downgraded this outcome to low quality (Summary of findings for the main comparison).

1.9 POCD: decline in cognitive function - one week

Six studies reported decline in cognitive function at one week (Casati 2005; Colak 2015; Mohandas 2013; Slater 2009; Vretzakis 2013; Zogogiannis 2011). We found that there was no significant difference between groups (n = 962, random-effects model, RR 0.62, 95% CI 0.37 to 1.04) (Analysis 1.3). This analysis indicated a high level of heterogeneity ($Chi^2 = 24.66$; P = 0.0002; $I^2 = 80\%$). Mohandas 2013 used a different type of monitoring equipment (Nonin Equanox) to the other studies (INVOS), which could potentially be the cause of the heterogeneity. After excluding Mohandas 2013, the analysis of the other five studies still showed no significant difference between groups (n = 862, random-effects model, RR 0.79, 95% CI 0.61 to 1.04). We downgraded this outcome from high quality to moderate due to the risk of bias with respect to incomplete outcome data (Colak 2015) (Summary of findings for the main comparison).

1.10 POCD: decline in cognitive function - 12 weeks

Two studies investigated this outcome at 12 weeks (Mohandas 2013; Slater 2009), but the result was heterogeneous when we attempted meta-analysis. We suspect that the heterogeneity was caused by the use of different monitoring equipment (Nonin Equanox in Mohandas 2013 versus INVOS in Slater 2009). We therefore presented these results separately without pooling. Mohandas 2013 favoured the active oxygenation group (odds ratio (OR) 0.01, 95% CI 0.00 to 0.21), whereas Slater 2009 showed no difference between groups (OR 0.96, 95% CI 0.51 to 1.81). We downgraded this outcome to low quality due to imprecision (small sample size) and inconsistency (Summary of findings for the main comparison).

1.11 POCD: cognitive tests - one week

Trafidlo 2015 (n = 43) used the Digit Span Test and reported a U statistic of 77.0 for overall numbers of forward and backward repetition (P = 0.003) and 82.5 for the Digit Span Test - forward (P = 0.005) at one week, favouring the use of active monitoring.

1.12 POCD: cognitive tests - four weeks

Trafidlo 2015 also reported a U statistic of 69.0 (P = 0.004) for the N-back Test (NBT 1 back) at four weeks, favouring the use of active monitoring.

Primary outcomes: intraoperative mortality or postoperative mortality

1.13 Intraoperative mortality or postoperative mortality

Regarding rate of death, we were able to pool data from three studies in a meta-analysis (Cowie 2014; Murkin 2007; Vretzakis 2013). We did not find a difference between active cerebral oxygenation monitoring and blinded cerebral oxygenation monitoring (n = 390, random-effects model, RR 0.63, 95% CI 0.08 to 5.03) (Analysis 1.4). We downgraded this outcome to low quality due to risk of bias (commercial funding) and imprecision (small sample size) (Summary of findings for the main comparison).

Secondary outcomes: the occurrence of abnormal $rScO_2$ during or after surgery

1.14 The occurrence of abnormal $rScO_2$ during or after surgery: desaturation

Seven studies provided data on desaturation in the operating room (Ballard 2012; Casati 2005; Cowie 2014; Deschamps 2013; Deschamps 2016; Murkin 2007; Slater 2009) and two studies in the intensive care unit (ICU) (Deschamps 2013; Deschamps 2016). We found that active cerebral near-infrared spectroscopy (NIRS) monitoring decreased the incidence of cerebral desaturation in the operating room (n = 916, random-effects model, RR 0.81, 95% CI 0.67 to 0.99) (Analysis 1.5). However, there was no significant difference in the occurrence of desaturation between the active cerebral oxygenation monitoring group and the blinded cerebral oxygenation monitoring group in the ICU (n = 249, random-effects model, RR 0.71, 95% CI 0.37 to 1.34) (Analysis 1.5).

1.15 The occurrence of abnormal $rScO_2$ during or after surgery: desaturation time

Harilall 2014 (n = 40) reported the desaturation time (minutes) during surgery. The result indicated a shorter duration of desaturation in the active cerebral oxygenation monitoring group than the blinded cerebral oxygenation monitoring group (MD -39.15, 95% CI -50.65 to -27.65) (Table 2).

1.16 The occurrence of abnormal $rScO_2$ during or after surgery: $rScO_2$ below 50%

In terms of the occurrence of rSO_2 below 50% during surgery, analysis of Ballard 2012 demonstrated that there was no significant difference between the active cerebral oxygenation monitoring group and the blinded cerebral oxygenation monitoring group (n = 65, RR 0.19, 95% CI 0.02 to 1.53) (Table 2).

1.17 The occurrence of abnormal $rScO_2$ during or after surgery: cerebral desaturation load (CDL) (%.min) or AUC $rScO_2$ (min, %)

Deschamps 2016 provided skewed data for the cerebral desaturation load (CDL) (%.min). The results demonstrated that active cerebral NIRS monitoring decreased the CDL either in the operating room (n = 102, 104 ± 217 versus n = 99, 398 ± 870) or in the ICU (n = 102, 454 ± 870 versus n = 99, 1070 ± 961).

The AUC $rScO_2$ (min, %) during surgery was reported by Mohandas 2013. The results indicated that the blinded monitoring group had significantly higher values (n = 100; right side (Rt) measurement, mean 2.993 ± standard deviation (SD) 8.87 in the active monitoring group versus 92.48 ± 58.31 in the blinded monitoring group; left side (Lt) measurement, 3.056 ± 8.96 versus 92.74 ± 58.61). The data were

skewed, therefore we did not combine together the means and SDs of both left and right side measurements.

1.18 The occurrence of abnormal $rScO_2$ during or after surgery: episodes of $rScO_2$ decrease (counts)

Trafidlo 2015 reported 2.46 ± 3.2 episodes of $rScO_2$ decrease in the active monitoring group (n = 13), but no data for the control group were provided.

1.19 The occurrence of abnormal $rScO_2$ during or after surgery: durations of $rScO_2$ decrease (minutes)

Trafidlo 2015 reported 7.46 ± 9.19 minutes' duration of $rScO_2$ decrease in the active monitoring group (n = 13), but no data for the control group were provided.

Secondary outcomes: any major non-neurological complications

1.20 Any major non-neurological complications as defined by the individual study

In terms of complications, we categorized eight studies into various outcomes as defined by the individual study (Casati 2005; Colak 2015; Cowie 2014; Lau 2012; Murkin 2007; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011) (Analysis 1.6).

For non-specific 'any reported complications' (i.e. only considering the total number of participants with complications regardless of the types of complications), meta-analysis of six studies demonstrated a similar rate of adverse events between the active cerebral oxygenation monitoring group and the blinded cerebral oxygenation monitoring group (n = 562, random-effects model, RR 0.76, 95% CI 0.58 to 1.00) (Analysis 1.6) (Casati 2005; Cowie 2014; Lau 2012; Murkin 2007; Trafidlo 2015; Vretzakis 2013).

In terms of non-specific respiratory complications, only Casati 2005 (n = 122) was included, which did not report a significant difference between groups (RR 0.29, 95% CI 0.03 to 2.56) (Analysis 1.6).

Three studies were in the analysis of non-specific cardiac complications (Casati 2005; Murkin 2007; Vretzakis 2013). Again, we did not find a difference between groups (n = 472, random-effects model, RR 0.80, 95% CI 0.28 to 2.31) (Analysis 1.6).

Two studies were included into analysis of non-specific renal complications (Colak 2015; Cowie 2014). The result did not indicate a difference between groups (n = 230, random-effects model, RR 0.87, 95% CI 0.27 to 2.76) (Analysis 1.6).

Among the other adverse events, we found a difference between groups in terms of the rate of major organ morbidity and mortality (MOMM) (n = 200, RR 0.33, 95% CI 0.08 to 0.95) (Analysis 1.6), but not for the others. This included surgical complications: rupture of the colonic anastomosis, mediastinitis, septicaemia, wound infection, reoperation for bleeding, surgical intervention, arrhythmia, myocardial infarction, cardiac arrest, pneumothorax and cardiac ischaemia (Analysis 1.6).

Secondary outcomes: ICU length of stay

1.21 Length of ICU stay (days)

Three studies were included in the analysis of length of ICU stay (Kara 2015; Mohandas 2013; Murkin 2007). We found that the use of active monitoring resulted in a shorter length of ICU stay than blinded cerebral oxygenation monitoring (n = 379, random-effects model, MD -0.29, 95% CI -0.48 to -0.09) (Analysis 1.7).

1.22 Length of ICU stay (hours/days)

Three studies provided the length of ICU stay as skewed data (Colak 2015; Deschamps 2013; Vretzakis 2013). Deschamps 2013 reported 71.9 ± 54.4 hours of ICU stay in the active monitoring group and 9.4 ± 49.3 hours in the control group. Colak 2015 and Vretzakis 2013 demonstrated no difference between groups in the length of ICU stay (in days) (2.7 ± 6.2 versus 1.9 ± 0.9 and 2.7 ± 3.8 versus 2.7 ± 3.6, respectively).

Secondary outcomes: hospital length of stay

1.23 Length of hospitalization (days)

One study was included in the analysis of length of hospitalization (Kara 2015). The result showed that the active cerebral NIRS monitoring group had a similar length of hospital stay to the conventional monitoring group (n = 79, MD -0.52, 95% CI -1.08 to 0.04) (Table 2).

1.24 Length of hospitalization (hours/days)

Four studies reported the length of hospitalization as skewed data or as the mean and range (Cowie 2014; Deschamps 2013; Murkin 2007; Vretzakis 2013). The results indicate that the active monitoring group had a similar length of hospital stay to the blinded monitoring group (Table 2).

Secondary outcomes: cost of hospitalization

No study reported this outcome.

Secondary outcomes: adverse events

No study considered this outcome.

Subgroup analysis: only primary outcomes

We conducted subgroup analyses by participants and interventions to explore the differences between them. However, none of the included studies included children (< 18 years) or compared perioperative cerebral NIRS monitoring versus other kinds of cerebral oxygenation monitoring. Therefore, we only investigated subgroups of the various types of surgery (i.e. carotid endarterectomy, cardiac or great vessel surgery with/without bypass, or other surgery) and the various active interventions (i.e. EQUANOX 7600 versus INVOS). We were unable to carry out subgroup analysis for neurosurgery because no study enrolled participants undergoing this type of surgery. We carried out the subgroup analyses for the pre-specified primary outcomes only.

Comparison 2: Subgroup of participants: participants undergoing cardiac or great vessel surgery, carotid endarterectomy or other surgery

We carried out the following subgroup analyses for subsets of studies with participants undergoing various types of surgery. Only Zogogiannis 2011 fell into the carotid endarterectomy subgroup; Colak 2015, Deschamps 2013, Deschamps 2016, Harilall 2014, Kara 2015, Lau 2012, Mohandas 2013, Murkin 2007, Slater 2009 and Vretzakis 2013 enrolled participants undergoing cardiac or great vessel surgery with/without bypass. Ballard 2012, Casati 2005, Cowie 2014 and Trafidlo 2015 considered other surgeries.

2.1 Postoperative stroke or other neurological injury: neurological injury

For this outcome, Colak 2015 considered cardiac or great vessel surgery and Casati 2005 fell into the other surgery group. Although the direction of effect favoured different interventions in these two studies, there was no statistical difference between interventions. Subgroup analysis of the results demonstrated no significant subgroup differences in postoperative neurological injury (Analysis 2.1). No data were available for the analysis of the carotid endarterectomy subgroup.

2.2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - one week

For this outcome, Mohandas 2013 considered cardiac or great vessel surgery and Ballard 2012 fell into the other surgery group. Subgroup analysis showed that there were no significant subgroup differences in MMSE score at one week after surgery (Analysis 2.2).

2.3 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks

Regarding this outcome, two studies enrolled participants undergoing cardiac or great vessel surgery (Lau 2012; Mohandas 2013) and one study considered other surgery (Ballard 2012). In either subgroup, active monitoring had a similar value at 12 weeks compared with blinded monitoring (Analysis 2.3), indicating no significant subgroup differences.

2.4 POCD as defined by the original studies - one week

For this outcome, Kara 2015 fell into the cardiac or great vessel surgery subgroup and Ballard 2012 the other surgery subgroup. In either subgroup, there was a significant difference between groups in mild POCD as defined by the original studies and but no difference in severe POCD at one week after surgery (Analysis 2.4; Analysis 2.5). We found no significant subgroup differences.

2.5 POCD: decline in cognitive function - one week

Regarding this outcome, four studies included participants undergoing the cardiac or great vessel surgery (Colak 2015; Mohandas 2013; Slater 2009; Vretzakis 2013), one study was in the carotid endarterectomy subgroup (Zogogiannis 2011) and one study fell into the other surgery subgroup (Casati 2005). Subgroup analysis of the data indicated no significant subgroup differences in terms of decline in cognitive function at one week after surgery. We did not find any significant difference between interventions in any of the subgroups (Analysis 2.6).

Comparison 3: Subgroup of interventions: cerebral oxygenation monitoring (EQUANOX) or INVOS versus blinded monitoring

Only Mohandas 2013 fell into the EQUANOX 7600 subgroup, and 13 studies were included in the comparison of INVOS versus blinded monitoring (Ballard 2012; Casati 2005; Colak 2015; Cowie 2014; Deschamps 2013; Harilall 2014; Kara 2015; Lau 2012; Murkin 2007; Slater 2009; Trafidlo 2015; Vretzakis 2013; Zogogiannis 2011). The multicentre study Deschamps 2016 used three types of rSO_2 monitoring devices including FORE-SIGHT, EQUANOX 7600 and INVOS in different centres, therefore it was not included in the subgroup analyses of interventions.

1. Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - one week

For this outcome, one study used the INVOS equipment (Ballard 2012) and one study used the EQUANOX equipment in the intervention group (Mohandas 2013). Compared with blinded monitoring, both INVOS and EQUANOX had higher MMSE scores at one week after surgery (Analysis 3.1). We found no significant subgroup differences.

2. Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks

In terms of MMSE score at 12 weeks after surgery, two studies considered the INVOS group (Ballard 2012; Lau 2012) and one study fell into the EQUANOX group (Mohandas 2013). The results indicated that compared with blinded monitoring, EQUANOX had higher MMSE scores at 12 weeks (n = 100, random-effects model, MD 3.16, 95% CI 0.98 to 5.34) but INVOS has similar scores (n = 79, random-effects model, MD 0.73, 95% CI -0.13 to 1.60) (Analysis 3.2).

3. POCD: decline in cognitive function - one week

Regarding this outcome, five studies employed the INVOS equipment (Casati 2005; Colak 2015; Slater 2009; Vretzakis 2013; Zogogiannis 2011) and one study employed the EQUANOX equipment (Mohandas 2013). The INVOS subgroup had a similar incidence of decline in cognitive function compared with the control group at one week (n = 862, random-effects model, RR 0.79, 95% CI 0.61 to 1.04) (Analysis 3.3). In the EQUANOX subgroup, compared with the control group, we found a lower incidence of participants with decline of cognitive function at one week (n = 100, RR 0.06, 95% CI 0.01 to 0.23) (Analysis 3.3).

Sensitivity analysis

1. Excluding studies at high risk of bias for allocation concealment

We did not conduct any sensitivity analysis because no study met the criteria for exclusion on the basis of inadequate allocation concealment.

2. Excluding studies at high risk of detection bias (blinding of outcome assessment)

One study was at high risk of detection bias (blinding of outcome assessment) and we excluded it from the analyses affected (Trafidlo 2015). After excluding Trafidlo 2015, the analysis with the other five studies showed a statistically significant and homogeneous effect estimate favouring the active oxygenation group (n = 537, random-effects model, RR 0.76, 95% CI 0.57 to 0.99) (Analysis 4.1; Analysis 4.2).

3. Excluding studies at high risk of attrition bias (missing data)

Three studies were at high risk of attrition bias and we excluded them from the affected analyses (Ballard 2012; Colak 2015; Lau 2012). The results indicated that there was no change as a result of their exclusion (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6; Analysis 5.7; Table 3).

4. Excluding studies at high risk of reporting bias

One study was at high risk of reporting bias and we excluded it from the affected analyses (Trafidlo 2015). The results indicated that there was a statistically significant but marginal difference between

the two groups after excluding Trafidlo 2015 (n = 537, random-effects model, RR 0.76, 95% CI 0.57 to 0.99) (Analysis 6.1; Analysis 6.2).

5. Excluding studies at high risk of other bias

Four studies were at high risk of other bias due to conflicts of interest, equipment grants and speaking honoraria (Ballard 2012; Cowie 2014; Deschamps 2016; Murkin 2007). We excluded these studies from the affected analyses. The results indicated changes in several outcomes after their exclusion (Analysis 7.7; Analysis 7.8; Table 4). The two groups had a similar mean MMSE score at 12 weeks after surgery (n = 118, random-effects model, MD 1.58, 95% CI -0.10 to 3.25) (Analysis 7.7). In terms of severe POCD as defined by the original studies up to one week, there was no significant difference between groups (n = 79, RR 0.12, 95% CI 0.01 to 2.25) (Table 4). We found no significant difference in the occurrence of desaturation between the active cerebral oxygenation monitoring group and the blinded cerebral oxygenation monitoring group in the operating room (n = 410, random-effects model, RR 0.88, 95% CI 0.69 to 1.13) (Analysis 7.8). There was no change in the remaining outcomes (Analysis 7.9; Analysis 7.10; Table 4).

Publication bias

Funnel plots of the primary outcome were not applicable due to the small number of studies involved in each meta-analysis.

Summary of findings

Using the principles of the GRADE system, we found a low-quality body of evidence associated with most of the primary outcomes, such as rate of postoperative stroke or other neurological injury, POCD and intraoperative or postoperative mortality (Summary of findings for the main comparison). We rated the quality of the evidence as moderate only for the decline in cognitive function (as defined by the individual study) at one week after surgery.

DISCUSSION

Summary of main results

We identified 15 studies comparing active cerebral oxygenation monitoring with blinded or no cerebral oxygenation monitoring during the perioperative period. These 15 studies comprised a total of 1822 adult participants.

For the primary outcomes, two studies with 312 participants reported postoperative neurological injury, however we did not pool the data because of clinical heterogeneity. Evidence from two studies in 240 participants demonstrated that active cerebral near-infrared spectroscopy (NIRS) monitoring showed little or no effect on the risk of postoperative stroke. Two studies with 126 participants showed that active cerebral NIRS monitoring may reduce the incidence of short-term mild postoperative cognitive dysfunction (POCD; as defined by the original studies) by 47% (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.30 to 0.95) and this difference was clinically important. Six studies with 962 participants provided moderate-quality evidence that active cerebral oxygenation monitoring probably does not decrease the occurrence of POCD (decline in cognitive function) at one week after surgery. There is uncertainty over postoperative delirium, intraoperative mortality and postoperative mortality.

In terms of secondary outcomes, seven studies comprising 916 participants demonstrated that active cerebral NIRS monitoring decreased the incidence of cerebral desaturation in the operating room by 19% (RR 0.81, 95% CI 0.67 to 0.99), but this difference was not clinically important. Three studies with 379 participants indicated that active cerebral NIRS monitoring shortened intensive care unit (ICU) length of stay by 0.29 days (mean difference (MD) -0.29, 95% CI -0.48 to -0.09), but this difference was not clinically important. However, the cost of hospitalization was not reported in any of the included studies. There is no evidence to determine whether routine use of NIRS-based cerebral oxygenation monitoring causes any adverse effects.

Overall completeness and applicability of evidence

None of the included studies in the review included a paediatric population or people undergoing neurosurgery. In addition, only two of the 15 included studies used cerebral NIRS monitoring in both the operating room and the ICU, whereas the others used it in the operating room. INVOS (Somanetics Corporation, USA) was used for the NIRS-based cerebral oximetry in most of the included studies. Some other kinds of cerebral NIRS monitor were not used in any of these studies.

With the exception of the cost of hospitalization and adverse events, all our other pre-specified primary outcomes and secondary outcomes were reported by the included studies. However, for some outcomes, such as postoperative stroke or other neurological injury and ICU length of stay, the evidence synthesis was based on a few studies with limited numbers of participants. As a result, further information will be required for the results to have internal and external validity.

The pooled data analyses in this review were limited mainly to cardiac or great vessel surgery with/without bypass. Consequently, extrapolating the results of the current meta-analyses to patients undergoing other types of surgery should be performed with caution and further high-quality clinical research is required.

Quality of the evidence

See also Risk of bias in included studies and Summary of findings for the main comparison.

We rated the quality of the evidence as low or moderate based on GRADE for most of the outcomes included in the review. We judged the evidence to be of low quality for postoperative mini-mental state examination (MMSE) or antisaccadic eye movement (ASEM) test scores due to risk of bias and the use of indirect measurement via a scale. We also rated the outcome of POCD as defined by the original studies and mortality as low-quality evidence due to several unclear risks of bias such as missing participant data and small sample sizes. For the outcome of decline in cognitive function at one week after surgery, we downgraded the level of the evidence to moderate quality due to the high risk of bias related to incomplete outcome data and selective reporting in Colak 2015.

Only one of the included studies was of good methodological quality (Vretzakis 2013). In the other studies, the most questionable bias was related to incomplete outcome data, selective reporting, unclear blinding status and other biases such as potential conflict of interest from industry sponsorship. In most of the included studies, the sample size was smaller than the optimal information size, which prompted us to downgrade the evidence for imprecision.

However, sensitivity analysis showed that missing data did not have an impact on the conclusions of this review. In this review, we did not create a funnel plot to qualitatively assess publication or reporting bias because fewer than 10 studies were included for each outcome.

Potential biases in the review process

We intended the search for studies to be as extensive as possible and we made every attempt to include international studies and not just those published in the English language. There remains the possibility that there may be other unpublished trials of this intervention (e.g. in the grey literature) that we do not currently have access to. This means that we may unwittingly have perpetuated a publication bias. Furthermore, one included study did not provide any email addresses for the study investigators (Harilall 2014). We attempted to conduct a comprehensive search for studies, but the fact that the studies meeting the inclusion criteria in an updated search have not yet been incorporated may be a source of potential bias. Despite this, our extensive search for complete and ongoing studies a strength of this review.

The definitions of cerebral desaturation were not identical in all the included studies, varying from below 70% of baseline values to below 90% of baseline values, which may potentially result in clinical heterogeneity. In addition, in Zogogiannis 2011, cerebral oximetry values were recorded in group B but anaesthesia management was not based on the algorithm mentioned in the full text; therefore, we only used the data from group A as the intervention group and group C as the control group, which may have a potential impact on the findings of the review.

Agreements and disagreements with other studies or reviews

A recently published systematic review discussed whether NIRS-based cerebral oxygenation monitoring could improve neurological outcomes in adults undergoing cardiac surgery (Zheng 2013). Only two randomized controlled trials (RCTs) and 40 other studies such as case reports and observational studies were included, but meta-analysis was not performed. Zheng 2013 identified two RCTs involving 440 participants. However, these two studies did not meet the eligibility criteria for our review, so we did not include them. In Zheng 2013, the authors concluded that there was insufficient evidence to demonstrate that interventions to improve intraoperative desaturation prevent stroke or POCD.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the evidence in our review, there is limited support for the use of perioperative active cerebral near-infrared spectroscopy (NIRS) monitoring of brain oxygenation in adults to reduce the occurrence of short-term mild postoperative cognitive dysfunction (POCD) and intensive care unit (ICU) length of stay. However, the difference is marginal and the quality of the evidence is low to moderate due to risk of bias, imprecision and inconsistency. We do not have sufficient evidence to determine the effects of active cerebral NIRS monitoring on postoperative neurological injury. There is low-quality evidence that active NIRS monitoring may lead to little or no decrease in postoperative stroke, delirium or death. We did not find any evidence of the adverse effects of the routine use of NIRS-based cerebral oxygenation monitoring. The 12 studies currently awaiting classification and the eight studies that are ongoing may alter the conclusions of this review when they are assessed.

Implications for research

We need more randomized controlled trials (RCTs) performed in those patients who are at high risk of cerebral ischaemia or hypoxia and are undergoing non-cardiac surgery, including neurosurgery, carotid endarterectomy and other surgery. Three ongoing studies have focused on shoulder surgery (Bal 2016), oesophagectomy (Shi 2013) and carotid surgery (Teurnier 2011), respectively. We also need RCTs performed in the paediatric population as none were identified by this review. We need future studies focusing on long-term outcomes as all the current completed RCTs were only concerned with acute postoperative variables. As NIRS technology develops, studies on newer NIRS-based cerebral oximetry may also be required. Moreover, economic outcomes such as the cost of hospitalization need to be included in future trials.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ballard 2012

Methods	**Design:** single-centre, 2-arm, parallel RCT **Period:** from March 2007 to January 2009 (with follow-up of the final participants until January 2010) **Follow-up:** 52 weeks **Settings:** 2 UK regional teaching hospitals
Participants	**Total N randomized:** N = 72 **Surgery type:** abdominal 12, orthopaedic 60 **Age:** mean 75.69 years, SD 7.40 (intervention group), mean 75.16 years, SD 6.51 years (control group) **Sex:** male 22, female 50 **Duration of surgery:** 127 (108 to 150) min, 133 (110 to 159) min **Inclusion criteria:** elective major abdominal or orthopaedic surgery under general anaesthesia; over 60 years of age; ASA classification ≤ 3; MMSE score ≥ 23; adequate English **Exclusion criteria:** unable to complete the outcome measures; Alzheimer's disease or other dementia; undergoing surgical procedures under regional anaesthesia; delirium at 1 week post surgery

Ballard 2012 *(Continued)*

Interventions	2 arms: **Intervention group (INVOS in OR):** depth of anaesthesia and rSO_2 were monitored in all participants using BIS and SICO respectively. Monitoring was performed in the OR throughout the procedure until extubation. An intraoperative management protocol was used to enable optimization of cerebral oxygen saturation (rSO_2) during surgery: bring BP to within 10% of baseline value using fluids or inotropes. If there is no change, maintain SpO_2 above 95% by increasing the percentage of inspired oxygen to 50%. If there is no change, end tidal carbon dioxide concentration increased to above 5.5%, avoiding excessive hypercarbia as well as hypocarbia. If there is no change, considering transfusion if the Hb level is less than 9 g.dl-1 where there is ongoing moderate to severe haemorrhage. If all the above fail to correct a decline then increase the $ETCO_2$ to 6% and increase the percentage of inspired oxygen to 100% N = 34 Device type: Somanetics Invos Cerebral Oximeter (SICO, Covidien inc, Co, USA) **Control group:** rSO_2 data were collected, but the anaesthetist was blinded to the monitoring data N = 38
Outcomes	Postoperative stroke or other neurological injury: cognitive function - MMSE, Vigilance Reaction Time, Trail Making, change data, at 1, 12 and 52 weeks postoperation Postoperative delirium (POD) or POCD: POCD at one, 12 and 52 weeks postoperation (see notes)* The occurrence of abnormal $rScO_2$ during or after surgery: desaturation**, rSO_2 below 50% during surgery - Unable to use: Postoperative stroke or other neurological injury: S100; only r value and P values of the relative analysis were reported
Notes	*Authors classified POCD as mild if there was a decline in performance in at least 1of the 7 cognitive domains (i.e. MMSE, simple reaction time, digit vigilance accuracy, digit vigilance reaction time, choice reaction time accuracy, choice reaction time and cognitive reaction time) by greater than 1standard deviation (SD); as moderate if there was an additional decline of at least 1.5 SD in an additional domain; and as severe if there was a decline of greater than 1.96 SD in at least 2 domains **rSO_2 drop > 15% baseline. The authors stated that the incidence of rSO_2 below 50% was 3.3% vs 17.1% in the intervention group vs the control group (1in the intervention group and 6 in the control group) (page 3; line 10-13, right). We calculated the total number of participants in each group and deduced that there were 30 and 35 participants in intervention group and control group respectively in this outcome assessment Funding source: funded by the National Institute for Health Research (NIHR) Declarations of interest: Quote: "David Green has received honoraria and expenses for meetings organized by Covidien Inc, manufacturers of the BIS and Invos monitors. Keith Wesnes has a commercial interest in the computerized cognitive assessment battery used in the trial—the Cognitive Drug Research battery. None of the others have any conflicts of interest" **Need to contact the author for further information:** the result of S100 in each group **Author contact details:** Prof. Clive Ballard Wolfson Centre for Age-Related Diseases, King's College London, London, United Kingdom Clive.ballard@kcl.ac.uk

Ballard 2012 *(Continued)*

Trial registration: ISRCTN39503939

We contacted Prof. Clive Ballard by email to request the missing data and detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation lists were generated by the study statistician in the statistical program package R..." (page 7, line 14-15, left) Comment: the authors gave sufficient information on the generation of randomization
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes containing the randomization codes were delivered to operating theatres, and an envelope selected randomly by the anaesthetist. The randomization envelope was opened only after the participant's eligibility and willingness to participate were re-confirmed prior to surgery." (page 7, line 16-21, left) Comment: sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The nested RCT trial was double-blinded; patients and researchers collecting outcome data were blind to treatment allocation. Only the anaesthetist delivering the intervention was aware of the treatment condition." The anaesthesia providers were unlikely to be blind to the treatment condition (page 7, line 10-13, left) Comment: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...researchers collecting outcome data were blind to treatment allocation." (page 7, line 11-12, left) Comment: blinding of outcome assessment ensured
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At 1 week after surgery, 11 and 9 participants declined assessment in intervention group and control group respectively. At 12 week after surgery, 6 and 4 participants declined assessment in intervention group and control group respectively. At 52 weeks after surgery, 6 and 6 participants declined assessment in intervention group and control group respectively." (page 3; Figure 1) Comment: the attrition rates in both groups at 1 week after surgery were 35.3% (intervention group) and 23.7% (control group) respectively, at 12 weeks were 20.6% and 10.5% respectively, at 52 weeks were 17.7% and 15.8% respectively. The proportion of missing outcomes, compared with observed events, is likely to induce important bias in the intervention effect estimate. No reasons for missing data provided.
Selective reporting (reporting bias)	Low risk	Comment: the authors did not report the "Trial Making" data at 1 week postoperatively. The authors did not present the S100B data in intervention group and control group. Only the r value and P value for the relative analysis were reported, however, these are unlikely to have had an important influence on the estimate of effects on the prespecified outcomes of this review.
Other bias	High risk	Quote: "David Green has received honoraria and expenses for meetings organised by Covidien Inc, manufacturers of the BIS and Invos monitors.

Ballard 2012 *(Continued)*

	Keith Wesnes has a commercial interest in the computerized cognitive assessment battery used in the trial—the Cognitive Drug Research battery." (page 1, line 28, abstract) Comment: 2 authors of this paper may have had conflicts of interest in this study

Casati 2005

Methods	**Design:** multicentre, 2-arm, parallel RCT **Period:** not reported **Follow-up:** not reported **Settings:** 5 university hospitals; the country is not reported
Participants	**Total N randomized:** N = 131 **Surgery type:** scheduled for major abdominal, nonvascular surgery under general anaesthesia (with an expected duration > 2 hours) **Age:** mean ˜73 years, SD ˜5 years **Sex:** male: 69, female: 53 **Duration of surgery:** intervention group: mean 259 min, SD 94 min, control group: mean 292 min, SD 100 min **Inclusion criteria:** "Patients older than 65 years, scheduled for major abdominal, nonvascular surgery under general anaesthesia (with an expected duration > 2 hours) were considered for the study." (page 741, line 32, left) **Exclusion criteria:** "Patients with pre-existing cerebral pathology (such as previous episodes of cerebral ischaemia or stroke) and ASA physical status> = Ⅳ or a baseline Mini Mental State Examination (MMSE) test <=23 and patients whose follow-up was not probable (not expected to be discharged alive from the hospital or with an expected hospital stay <4 days) were excluded." (page 741, line 40, left)
Interventions	2 arms: **Intervention group (INVOS in the OR):** the INVOS monitor in the OR was visible and anaesthesia management was aimed at maintaining rSO_2 more than 75% of baseline values. In case of cerebral desaturation in the intervention group, the attending anaesthesiologist activated a 2-step treatment: The first step included checking the ventilator, head position and tubing system, increasing FiO_2, increasing end-tidal CO_2 partial pressure if the $ETCO_2$ was < 35 mmHg, and increasing arterial blood pressure with intravascular fluid administration (250 mL hetastarch) and vasoconstrictors (ethylephrine 2 mg to 5 mg IV) if systolic arterial blood pressure was <= 90 mmHg. If the first step did not restore acceptable rSO2 values within 60 seconds, the second step included the reduction of brain oxygen consumption with an IV bolus of propofol (0.5 mg/kg) N = 63 Device type: Somanetics Invos Cerebral Oximeter (SICO, Covidien inc, Co, USA) **Control group:** in the control group the screen of the INVOS monitor was blinded and general anaesthesia was managed routinely maintaining arterial blood pressure and heart rate values within 20% of baseline values. N = 68
Outcomes	POCD: decline of cognitive function at the 7th day postoperation* (see notes)

Casati 2005 *(Continued)*

	Postoperative stroke or other neurological injury: neurological injury Intraoperative mortality or postoperative mortality: death The occurrence of abnormal $rScO_2$ during or after surgery: desaturation** (see notes), mean rSO_2 Any major non-neurological complications - Unable to use: The occurrence of abnormal $rScO_2$ during or after surgery: AUC rSO_2< 50%, AUC rSO_2< 75% Length of hospital stay: the authors did not report data for this outcome
Notes	*A decrease in MMSE score of more than 2 points from baseline was also considered as an index of decline in cognitive function **Cerebral desaturation was considered to occur when rSO_2 values decreased to < 75% of baseline values for 15 seconds. If baseline rSO_2 was less than 50%, the threshold for defining cerebral desaturation was a reduction to less than 80% of baseline values Funding source: the study was entirely supported by funding of the 5 hospitals only Declarations of interest: not reported Need to contact the author for the setting information **Author's contact information:** Andrea Casati, MD, Department of Anesthesiology, Azienda Ospedaliera di Parma, Via Gramsci 14 – 43100 Parma Email: acasati@ao.pr.it (page 740 footnote) We contacted Dr. Andrea Casati by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "According to a computer-generated sequence of numbers and using a sealed envelope technique, patients were randomly allocated to two groups". (page 741, line 3, right) Comment: the authors gave sufficient information on the generation of randomization
Allocation concealment (selection bias)	Low risk	Quote: "According to a computer-generated sequence of numbers and using a sealed envelope technique, patients were randomly allocated to two groups." (page 741, line 3, right) Comment: sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... discharge by the surgeons, ward nurses, and research fellows, who were blinded as to intraoperative management and patient grouping..." (page 742, line 26, left) Comment: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken

Casati 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "... discharge by the surgeons, ward nurses, and research fellows, who were blinded as to intraoperative management and patient grouping..." (page 742, line 26, left) Comment: research fellows maybe the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: page 743, figure 1 Comment: 131 participants were randomized. 1 participant in the intervention group was excluded because of insertion of epidural catheter, 3 cases were excluded because of cancellation and another 3 cases were excluded because of technical failure In the control group, 1 participant was excluded because of insertion of epidural catheter and a further 1 case was excluded because of technical failure. 1participant in the control group died 20 days after surgery because of surgical complications (rupture of the clonic anastomosis) Comment: reasons for missing outcome data are unlikely to be related to the interventions
Selective reporting (reporting bias)	Unclear risk	Comment: we did not have enough information to confidently conclude the status of selective reporting
Other bias	Low risk	Quote: "The study was entirely supported by funding of the five hospitals only." (page 740, line 20, right) Comment: none obvious

Colak 2015

Methods	**Design:** 2-arm, parallel RCT **Period:** June 2009 to September 2011 **Follow-up:** 6 participants in the INVOS group and 4 in the control group did not receive the allocated intervention after randomization (protocol violation). 9 participants (6 in the INVOS group and 3 in the control group) did not perform control cognitive test after surgery (lost to follow-up) **Settings:** university hospital centre, Croatia
Participants	**Total N randomized:** N = 200 **Surgery type:** on-pump CABG surgery with the use of cardiopulmonary bypass **Age:** 61.9 ± 7.1 in the INVOS group; 63.4 ± 8.8 in the no monitoring group **Sex:** male: 148, female: 42 (10 participants lost to follow-up) **Duration of surgery:** bypass time, intervention group: mean ± SD ˜91 ± 31 min, control group: 89 ± 32 min Aortic cross-clamp time, intervention group: mean ± SD ˜63 ± 23 min, control group: 62 ± 26 min **Inclusion criteria:** "Two hundred participants between 40 and 80 years who underwent on-pump CABG surgery and signed informed consent were included in the study" **Exclusion criteria:** "… significant carotid artery stenosis, previous stroke or head injury, seizure, psychiatric illness, decompensated heart failure (NYHA Ⅲ/Ⅳ), left ventricular ejection fraction less than

Colak 2015 *(Continued)*

	25%, emergency cardiac surgery, off-pump CABG, severely impaired renal and liver function, who refuse to participate, reoperations, and dialysis"
Interventions	2 arms: **Intervention group (INVOS in the OR):** Quote: "Patients were randomized into the interventional INVOS group, in which rSO2 was maintained above 80% of patient's baseline value during the operation…During surgery, patients involved in the INVOS group were monitored by cerebral oximetry using the INVOS system...All patients in the INVOS group were monitored with the INVOS system (INVOS 5100C; Somanetics Corp., Troy, MI, USA). The INVOS system uses NIRS for non-invasive and continuous measurement of changes in cerebral oxygen saturation. The probes for INVOS cerebral oxygen monitoring were attached bilaterally on the patient's forehead overlying the frontal–temporal region to awaken patients who breathed oxygen by nasal catheter, just before induction of anaesthesia. A baseline regional cerebral oxygen saturation (rSO_2) value for each side of the brain was determined a short time after probes were attached. The rSO_2 values were displayed on a screen and recorded during the entire surgery. If the rSO_2 during surgery decreased below 80% of baseline value or below 50% of absolute value, we responded with standardized interventions to maintain rSO_2 above those values. These interventions involved measures to eliminate mechanical obstruction to cerebral flow (repositioning of head or bypass cannulae), to increase cerebral oxygen delivery (increasing FiO_2, pCO_2, mean arterial pressure, cardiac output or pump flow and haematocrit) or to reduce cerebral oxygen consumption (increasing of anaesthetic depth and reduction of temperature)". N = 100 Device type: INVOS system (INVOS 5100C; Somanetics Corp., Troy, MI, USA) **Control group:** Quote: "Patients in the CONTROL group were not monitored with cerebral oximetry and only standardized monitoring in cardiac surgery was utilized." N = 100
Outcomes	Postoperative stroke or other neurological injury: neurological deficit (coma, stupor, transient ischaemic attack (TIA), stroke) Postoperative delirium (POD) or POCD: postoperative cognitive impairment Postoperative delirium (POD) or POCD: postoperative delirium Myocardial infarction Atrial fibrillation Prolonged mechanical ventilation Haemodialysis Infection Revision Hospital stay > 7 days (% of patients) ICU length of stay (in days)
Notes	Funding source: the financial support was provided by institutional sources, University of Zagreb Declarations of interest: Quote: "Conflict of interest: none declared" **Author's contact information:** Corresponding author: Dr. Z. Colak

Colak 2015 *(Continued)*

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We contacted Dr. Zeljko Colak by email to request the missing data and detailed information for the study. He provided the reasons for dropouts and explained the differences between the full text and ClinicalTrials.org.

Quote: "In our study, only patients who underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass were included. Of the 200 randomized patients, 10 of them (4 participants in Control group and 6 participants in INVOS group) were not analysed because they did not receive allocated surgical intervention (CABG), due to changes in intraoperative plan (e.g. additional valvular surgery).
Of the remaining 190 patients, 9 of them did not perform control cognitive test (7th postoperative day) because they were lost in follow-up: 3 participants in Control group – because they were transferred to another hospital and 6 participants in INVOS group – because 4 were transferred to another hospital and 2 declined to participate.
You can also see "Figure 1 - Flow diagram of patients allocated in the study" in our manuscript published in EJCTS 47(2015) 447-454.
In the manuscript, data regarding postoperative complications (delirium, atrial fibrillation...) are presented as percentage of the whole number of patients in that group, while data reported in the "Clinical Trials Gov" are presented as number of participants. That is why the difference occurs."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All patients were randomly assigned into the INVOS group or the CONTROL group using a computerized random number generator" (page 488) Comment: using a computerized random number generator
Allocation concealment (selection bias)	Low risk	Quote: "After informed consent was obtained, an enclosed assignment in a sequentially numbered, opaque, sealed envelope was allocated to each patient" (page 488) Comment: an enclosed assignment in a sequentially numbered, opaque, sealed envelope was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The anaesthesiologists who performed anaesthesia and interventional protocol for maintaining of cerebral oxygenation were involved neither in data collection nor in cognitive test results of patients. Investigators who performed cognitive tests were blinded to patient's allocation. Patients were also blinded to the allocation group" (page 488) Comment: the anaesthesiologists who performed anaesthesia and the interventional protocol for maintaining cerebral oxygenation were involved neither in data collection nor in the cognitive test results of patients. Patients were also blinded to the allocation of groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the investigators who performed the cognitive tests were blinded to the patient's allocation
Incomplete outcome data (attrition bias)	High risk	Comment: of the 200 participants, only 181 (90.5%) had neurocognitive tests at 7 days after surgery. The authors did not report the reasons for dropouts.

Colak 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: none obvious
Other bias	Low risk	Comment: none obvious

Cowie 2014

Methods	**Design:** 2-arm, parallel RCT **Period:** February 2012 to September 2012 **Follow-up:** no dropouts **Settings:** hospital in Victoria, Australia
Participants	**Total N randomized:** N = 40 **Surgery type:** total knee or hip replacement or bowel resection surgery **Age:** mean (95% CI) 78.0 (75.4 to 80.5) years in the intervention group; 77.5 (75.6 to 79.5) in the control group **Sex:** male: 20, female: 20 **Duration of surgery:** mean (95% CI) intervention group: 141 (118 to 164) min; control group: 187 (141 to 233) min **Inclusion criteria:** patients over the age of 70 years undergoing total knee or hip replacement or bowel resection surgery **Exclusion criteria:** emergency or unplanned surgery or the inability to provide informed consent for participation
Interventions	2 arms: **Intervention group (INVOS in the OR):** If the participant was randomized to the intervention group (Group I), the anaesthetist was able to monitor the ScO_2 throughout the operation. The anaesthetists were instructed to maintain the ScO_2 within 25% of the participant's baseline value, which was taken following induction of anaesthesia ... The anaesthetist was provided with a list of suggested methods to improve ScO_2, such as avoiding obstruction of neck veins and optimizing mean arterial pressure, oxygen saturation, end-tidal carbon dioxide and haemoglobin concentration. The use and timing of these interventions was left entirely to the choice of the anaesthetist ... to monitor the ScO_2 throughout the operation. The anaesthetists were instructed to maintain the ScO_2 within 25% of the participant's baseline value, which was taken following induction of anaesthesia ... At the conclusion of the operation, the cerebral oximetry monitor was turned off prior to leaving the operating theatre. N = 20 Device type: Covidien USA (Mansfield, MA) **Control group**: If the participant was randomized to the control group (Group C), the monitor was covered throughout the case. N = 20
Outcomes	Postoperative stroke or other neurological injury: postoperative stroke Postoperative mortality Postoperative acute myocardial infarction

Cowie 2014 *(Continued)*

	Postoperative cardiac arrest Postoperative acute pulmonary oedema Postoperative pulmonary embolism Postoperative acute renal failure Cerebral desaturation rates Length of hospital stay Wound infection Unplanned HDU/ICU admission Management of hypotension without cerebral oximetry reasons Total number of complications
Notes	Funding source: Quote: "This study was supported by an equipment grant (device loan and sensors) from Covidien USA (Mansfield, MA) and also by an Australian and New Zealand College of Anaesthetists pilot trial grant." Declarations of interest: not reported **Author's contact information:** Corresponding author: Dr. Dean Cowie MB BS, FANZCA, Staff Specialist, Department of Anaesthesia, Austin Health, Heidelberg, Victoria, Australia Email: dean.cowie@austin.org.au We contacted Dr. Dean Cowie by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomised to one of two groups using a random number allocation system with permuted blocks" (page 311) Comment: using a random number allocation system with permuted blocks
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients were blinded to group allocation, as were all investigators analysing the data" (page 312) Comment: all patients were blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients were blinded to group allocation, as were all investigators analysing the data...complications were recorded by blinded investigators via daily visits to the patient on postoperative days 1 to 5, as well as a review of the patient records, pathology tests and radiology results" (page 312) Comment: outcomes were assessed blindly
Incomplete outcome data (attrition bias)	Low risk	Comment: no participants left the study early during the period of study

Cowie 2014 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: none obvious
Other bias	High risk	Comment: this study was supported by an equipment grant (device loan and sensors) from Covidien USA (Mansfield, MA) and also by an Australian and New Zealand College of Anaesthetists pilot trial grant

Deschamps 2013

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Follow-up:** not reported **Settings:** tertiary care centre specializing in cardiac surgery, Canada
Participants	**Total N randomized**: 48 **Surgery type:** complex cardiac surgery with cardiopulmonary bypass (CPB), except for patients with planned circulatory arrest **Age:** mean 71.1 years, SD 7.9 years **Sex:** male 33, female 15 **Duration of surgery:** intervention group: mean 322.6 min, SD 159.2 min; control group: mean 305.7 min, SD 71.5 min **Cardiopulmonary bypass time:** mean 119.3 min, SD 39.6 min **Inclusion criteria:** consecutive patients requiring complex cardiac surgery with CPB regardless of comorbidities, including following 3 situations: 1. High-risk surgery (defined as redo surgery, adult congenital surgery, thoracic aortic surgery with and without circulatory arrest and combined procedures surgery) 2. Combined surgery, including coronary artery bypass graft and valvular surgery or multiple valvular surgery or valvular and aortic surgery 3. Patients with a perioperative risk estimation score > 15 using the Parsonnet score **Exclusion criteria:** patients under the age of 18; emergency surgery; first time CABG surgery; single-valve surgery in patients with a perioperative risk estimation score < 15; patients with planned circulatory arrest (because the anaesthesiologists and surgeons insisted on the use of NIRS in these cases)
Interventions	2 arms: **Intervention group:** INVOS in the OR and ICU: rSO_2 monitoring in the OR and ICU. The algorithmic approach published previously was followed to reverse significant decreases in rSO_2 (Denault 2007). Device type: INVOS 4000 N = 23 **Control group:** rSO_2 was recorded, but "NIRS values were hidden from the anesthesiologists" N = 25

Deschamps 2013 *(Continued)*

Outcomes	The occurrence of abnormal $rScO_2$ during or after surgery: desaturation* (OR and ICU) - Unable to use: Duration of mechanical ventilation postoperatively: skewed data (we did not plan to observe this outcome in our protocol) ICU length of stay: skewed data; we present these data as 'other data' in the data analysis section Hospital length of stay: skewed data, we present these data as 'other data' in the data analysis section
Notes	*Significant decreases in rSO_2 values were defined as a decrease > 20% from baseline lasting 15 seconds or more Funding source: funded by a grant from the Research Foundation of the Anesthesiology Department of the Université de Montréal and the Foundation of the Montreal Heart Institute Declarations of interest: not reported Corresponding author: Dr. Alain Deschamps PhD, MD, Department of Anesthesiology, Montreal Heart Institute, Université de Montreal, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada Email: a.deschamps@umontreal.ca We contacted Dr. Alain Deschamps by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomized into 2 groups..." (page 1260, line 13-21, right) Comment: there was no further description of randomization methods, but we accept the authors' reporting as true and accurate
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was inadequate information about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no missing data
Selective reporting (reporting bias)	Unclear risk	Comment: the authors did not clarify the expected outcomes for the randomized pilot study in the methods section. However, they reported important outcomes such as the incidence of cerebral desaturation, ICU and hospital length of stay, and postoperative complications in the 2 study groups.
Other bias	Low risk	Comment: none obvious

Deschamps 2016

Methods	**Design:** 2-arm, parallel RCT **Period:** between April 2012 and October 2013 **Follow-up:** 30 days postoperatively **Settings:** 8 Canadian centres; however, detailed information about these hospitals was not presented
Participants	**Total N randomized**: 201 **Surgery type:** high-risk surgery defined as combined surgery (coronary bypass plus valve replacement or repair), or multiple valve replacement and/or redo surgery **Age:** mean 71 years, SD 11.2 years **Sex:** male 145, female 56 **Duration of surgery:** unclear **Cardiopulmonary bypass time**: mean 135.9 min, SD 54.2 min Aortic cross clamp time: mean 105.8 min, SD 42.4 min **Inclusion criteria:** age over 18 years, had a cumulative EuroScore II more than or equal to 10, and/or were undergoing high-risk surgery defined as combined surgery (coronary bypass plus valve replacement or repair), or multiple valve replacement and/or redo surgery **Exclusion criteria:** unable to read French or English, undergoing off-pump coronary artery bypass surgery, emergency surgery (i.e. less than 6 hours after diagnosis) or planned deep hypothermic circulatory arrest, acute endocarditis, or the presence of active delirium or encephalopathy
Interventions	2 arms: **Intervention group:** (In the OR and ICU): patients allocated to the intervention group had NIRS values displayed on the monitor. At an intervention threshold of a 10% decrease in rSO_2 value relative to baseline for a duration exceeding 15 seconds, anaesthesiologists used an interventional algorithm to reverse desaturations Device type: research sites used 1 of the 3 Health Canada approved rSO_2 monitoring devices for the study: FORE-SIGHT (CAS Medical Systems Inc., USA; 1 site, 9% of participants), EQUANOX Classic 7600 (Nonin Medical Inc., USA; M, 2 sites, 28% of participants) and INVOS 5100C-PB (Covidien, USA; 5 sites, 62% of participants) N = 102 **Control group:** patients allocated to the control group had cerebral oximetry probes applied to the forehead but did not have NIRS values displayed on the monitor (i.e. anaesthesiologists were blinded to rSO_2 values). Anaesthesiologists relied on standard monitoring for the management of these cases N = 99
Outcomes	The incidence of decreases in rSO_2 more than 20% of baseline in the first 12 hours in the ICU (or until tracheal extubation) Cerebral desaturation below 10% relative to baseline in the operating room - Unable to use: Cerebral desaturation load (CDL) (%.min)* (see notes): skewed data; we present these data as 'other data' in the data analysis section Major organ morbidity and mortality (MOMM) score; a composite endpoint of stroke, renal failure requiring dialysis, prolonged mechanical ventilation for more than 48 hours, deep sternal wound infection, reoperation and death; length of hospital stay: for these outcomes, authors only reported data for

Deschamps 2016 *(Continued)*

	participants without cerebral desaturations and for participants with cerebral desaturations in the control group and the intervention group. They did not provide data for all participants in the intervention group and the control group, respectively
Notes	Funding source: funded in part by the Canadian Anesthesia Research Foundation (Toronto, Ontario, Canada); the Montreal Heart Institute Foundation (Montreal, Quebec, Canada); and the Anesthesiology Departments of the University of Manitoba (Winnipeg, Manitoba, Canada), Ottawa Heart Institute (Ottawa, Ontario, Canada), McMaster University (Hamilton, Ontario, Canada), University of Calgary (Calgary, Alberta, Canada), University of Alberta (Edmonton, Alberta, Canada), and the University of British Columbia (Vancouver, British Columbia, Canada) Declarations of interest: "Dr. Deschamps has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by the companies Nonin Medical Inc., Plymouth, Minnesota, and Covidien Inc. (now a part of Medtronic), Boulder, Colorado. Dr. Denault has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by Covidien Inc. (now a part of Medtronic). NONIN Medical Inc. provided equipment and sensors for one of the centres implicated in the study. The other authors declare no competing interests." *CDL, defined as the cumulative area under the curve of desaturation over time for decreases in rSO_2 values below 20% relative to baseline Corresponding author: Dr. Deschamps Department of Anesthesiology, Montreal Heart Institute, 5000 rue Bélanger, Montreal, Quebec, Canada H1T 1C8 Email: a.deschamps@umontreal.ca; deschamps.a@gmail.com Trial registration: https://clinicaltrials.gov/ct2/show/NCT01432184 We contacted Dr. Alain Deschamps by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed in a 1:1 ratio using a computer-generated random number table with permuted random blocks stratified by hospital sites" Comment: a computer-generated random number table was used to generate the random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...the ICU staff (blinded to group assignment)" Comment: the blinding of participants and other staff members was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was inadequate information about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Follow-up to 30 days was successful in all 201 patients in the study" Comment: there were no missing data

Deschamps 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes were reported
Other bias	High risk	Quote: "Dr. Deschamps has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by the companies Nonin Medical Inc., Plymouth, Minnesota, and Covidien Inc. (now a part of Medtronic), Boulder, Colorado. Dr. Denault has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by Covidien Inc. (now a part of Medtronic). NONIN Medical Inc. provided equipment and sensors for one of the centres implicated in the study." Comment: there might be a conflict of interest, but we do not have enough information to determine

Harilall 2014

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Follow-up:** not reported **Settings:** Inkosi Albert Luthuli Central Hospital, South Africa
Participants	**Total N randomized**: N = 40 **Surgery type:** undergoing elective on-pump coronary artery bypass graft surgery **Age:** mean 55.3 years, SD 9.7 years **Sex:** male 28, female 12 **Cardiopulmonary bypass time**: mean 133.3 min, SD 26.86 min Cross clamp time: mean 80.08 min, SD 17.78 min **Inclusion criteria:** age over 18 years, scheduled for elective on-pump coronary artery bypass graft surgery and a preoperative haematocrit greater than 36% (haemoglobin > 12 g/dl) **Exclusion criteria:** ...pregnancy, history of stroke or persistent neurological residue, history of transient ischaemic attack (TIA), unilateral stenosis of carotid artery greater than 70%, bilateral stenosis of carotid artery greater than 50%, combined cardiac procedure, i.e. CABG plus heart valve replacement, left ventricular ejection fraction less than 40%, left main stem stenosis more than 70%, symptomatic chronic pulmonary disease requiring long term medication, renal insufficiency or anuric renal failure or creatinine above 1.5 mg/dl, HIV positive patients, patients in AF (atrial fibrillation), patients presenting with left ventricular thrombosis preoperatively, presence of aortic atheroma detected pre, intra or postoperatively
Interventions	2 arms: **Intervention group:** (INVOS in the OR): in the interventional group, rSO_2 monitoring in the OR, intraoperative regional cerebral oxygen saturation (rSO_2) monitoring was performed with active display and administration of the Murkin treatment interventional protocol (Murkin 2007) Device type: Somanetics INVOS model 5100c cerebral/Somanetics oximeter (Covidien, Midrand South Africa) N = 20

Harilall 2014 *(Continued)*

	Control group: in the control group, regional cerebral oxygen saturation monitoring was not visible to the cardiovascular perfusionist operating the heart lung machine during cardiopulmonary bypass (blinded) N = 20
Outcomes	The occurrence of abnormal $rScO_2$ during or after surgery: desaturation* time (see notes) - Unable to use Postoperative stroke or other neurological injury: change in serum S100B: skewed data; we present these data as 'other data' in the data analysis section
Notes	Funding source: not reported Declarations of interest: not reported *Cerebral desaturation was defined as a decrease in oxygen saturation values below 70% of baseline for more than 1 min Corresponding author: Dr. Jamila Kathoon Adam Department of Biomedical and Clinical Technology, Durban University of Technology, South Africa Tel.: +27 31 373 5291 Fax: +27 31 373 5295 Email: not presented in the article We contacted Dr. Jamila Kathoon Adam by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised into intervention and control groups, and the completeness of the randomisation process was checked statistically by comparison of baseline features between the two groups using t-tests in the case of quantitative variables and Pearson's chi square tests or Fisher's exact tests for categorical variables" (page 70, line 55-56, right page 71, line 1-5, left) Comment: the authors reported that patients were randomly assigned to either group and the randomization produced balanced baseline characteristics
Allocation concealment (selection bias)	Low risk	Quote: "... using a sealed envelope system." (page 69, line 32, left) Comment: sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data

Harilall 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes were reported
Other bias	Low risk	Comment: none obvious

Kara 2015

Methods	**Design:** 2-arm, parallel RCT **Period:** December 2013 to February 2015 **Follow-up:** not reported **Settings:** in a tertiary healthcare centre, Turkey
Participants	**Total N randomized:** N = 79 **Surgery type:** coronary artery bypass grafting (CABG) operation with asymptomatic carotid artery disease for whom no intervention is intended (carotid artery stenosis is between ≥ 50% and < 70% on Doppler ultrasonography (USG)) **Age:** NIRS group: mean 59.1 years, SD 9.4 years; no NIRS group: mean 61.2 years, SD 10.3 years **Sex:** NIRS group: male 33, female 10; no NIRS group: male 29, female 7 **Cardiopulmonary bypass time:** NIRS group: mean 77.7 min, SD 28.3 min; no NIRS group: mean 78.6 min, SD 26.9 min Aortic cross clamp time: NIRS group: mean 48.8 min, SD 23.1 min; no NIRS group: mean 56.3 min, SD 25.8 min **Inclusion criteria:** participants who had coronary artery bypass grafting (CABG) operation with asymptomatic carotid artery disease for whom no intervention is intended (carotid artery stenosis is between ≥ 50% and < 70% on Doppler ultrasonography (USG)) **Exclusion criteria:**patients who had an additional procedure other than CABG, who had a ascending aortic atherosclerosis degree of ≥ 2, carotid artery stenosis ≥ 70% lesions on carotid Doppler USG, who had a low level of literacy, who had a clinical history of cerebrovascular attack, fit and who had psychiatric disorders
Interventions	2 arms: Intervention group (NIRS group) **(**INVOS in the OR): intraoperative near-infrared spectroscopy was applied. The algorithm used was the standard that is suggested for the brain oxymetry use when there is a > 20% decrease in the rSO_2 values of the NIRS group patients during CPB when compared to their initial values (Akpek 2008) Device type: INVOS 5100C; Somanetics Corp, Troy, MI, USA N = 43 Control group (no NIRS group): intraoperative near-infrared spectroscopy was not applied N = 36
Outcomes	Postoperative cognitive function impairment (mild impairment; serious impairment) Intensive care and duration of hospital stay - Unable to use:

Kara 2015 *(Continued)*

	rSO_2 parameters: the authors did not report these data
Notes	Funding source: not reported Declarations of interest: no conflict of interest Corresponding author: Ibrahim Kara, MD Address: Adnan Menderes Cad., Saglık Sok., No: 195, Adapazarı, 54000, Sakarya, Turkey Email: ikara7881@hotmail.com We contacted Dr. Ibrahim Kara by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization list has been generated by the clinic head nurse and the patients were sent to the surgery in accordance with such list..." Comment: the authors mentioned use of a randomization list but did not provide the detailed methods of randomization; in this case we accepted the authors' reporting as true and accurate
Allocation concealment (selection bias)	Low risk	Quote: "… the randomization list was kept hidden until the study is concluded" Comment: the authors mentioned allocation concealment but did not state the methods of allocation concealment in detail; in this case we accepted the authors' reporting as true and accurate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "... randomized, controlled and with a double blind working design ..." Comment: the authors stated that a double-blind working design was used. However, the blinding of participants and other staff members was not clearly described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Preoperative and postoperative cognitive test has been applied to all the patients by two perfusionists under the supervision of the neurologist in accordance with the randomization list of the head nurse and it has been evaluated by two observers by using double blind method" Quote: "... rSO2 changes of the patients during cardiopulmonary bypass (CPB) have been recorded in excel format in computer environment by the perfusionist and were evaluated by two observers with double blind method" Comment: blinding of outcome assessment ensured for the subjective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Unclear risk	Comment: intraoperative rSO_2 parameters were not reported
Other bias	Low risk	Comment: none obvious

Lau 2012

Methods	**Design:** 2-arm, parallel RCT **Period:** November 2009 to September 2011 **Follow-up:** not reported **Settings:** hospital (detailed information was not given)
Participants	**Total N randomized:** N = 25 **Surgery type:** aortic surgery **Age:** mean ± SD, intervention group: 60.5 ± 9.4 years; control group: 62.3 ± 11.5 years **Sex:** male: 15, female: 10 **Duration of surgery:** unclear **Inclusion criteria:** 18 to 80 years; adult male and female patients 18 to 80 years of age scheduled for aortic surgery requiring deep hypothermic circulatory arrest (DHCA) and intention to use antegrade selective cerebral perfusion with or without retrograde cerebral perfusion (RCP) **Exclusion criteria:** adult male and female patients 18 to 80 years of age undergoing aortic surgery not scheduled for DHCA; patients with ejection fraction < 15%; pregnancy; prisoners; patients mentally impaired (screening criteria i.e. MMSE score ≤ 23); history of stroke
Interventions	2 arms: **Intervention group (INVOS in the OR):** INVOS cerebral oximetry monitoring Intervention will be initiated if rSO_2 drops > 20% from baseline or rSO_2 declines below 50% Sequence of interventions to increase cerebral oxygen saturation 1. Check head and cannula position 2. Increase mean arterial pressure 3. Increase pump flow 4. Increase systemic oxygenation 5. Increase $PaCO_2$ > 45 6. Increase anaesthetic depth by increasing volatile anaesthetic or by administering propofol boluses 7. Consider PRBC transfusion for Hct < 21% N = 12 **Device type:** INVOS Somanetics Cerebral Oximeter (USA) **Control group:** blinded cerebral oximetry monitoring with no intervention in surgical procedures and anaesthesia without deviation from standard of care INVOS cerebral oximetry blinded monitoring with no deviation in surgical procedures or standard of care in anaesthesia N = 13
Outcomes	Adverse events Postoperative stroke or other neurological injury: Mini Mental State Examination (MMSE)
Notes	This is an ongoing trial with results presented in ClinicalTrials.gov (NCT01149148)

Lau 2012 *(Continued)*

	Funding source: the study was supported by the University of Michigan Declarations of interest: not reported **Author's contact information:** Corresponding author: Lau WC, MD Wei C. Lau, University of Michigan Health System Phone: 734 9369479 Email: weiclau@med.umich.edu We contacted Dr. Wei C. Lau by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: allocation was stated as randomized, but no further description provided
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind (subject, caregiver, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: double-blind (subject, caregiver, investigator)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2 of 12 in the intervention group and 3 of 13 in the control group dropped out, but MMSE was analysed with 9 participants in each group
Selective reporting (reporting bias)	Low risk	Comment: all prespecified outcomes were reported
Other bias	Low risk	Comment: none obvious

Mohandas 2013

Methods	**Design:** single-centre, 2-arm, parallel RCT **Period:** not reported **Follow-up:** not reported **Settings:** not reported
Participants	**Total N randomized:** N = 100 **Surgery type:** undergoing cardiac surgery using CPB **Age:** mean 38.05 years, SD 15.81 years

Mohandas 2013 *(Continued)*

	Sex: male 58, female 42 **CPB time:** mean 86.28 min, SD 35.80 min **AoX time:** mean 65 min, SD 28.74 **Inclusion criteria:** patients undergoing cardiac surgery using CPB were selected for the study **Exclusion criteria:** patients with pre-existing neuropsychiatric disorders, inability to correctly perform the neurocognitive tests and mini mental state examination (MMSE) scores of less than 23, were excluded from the study
Interventions	2 arms: **Intervention group (Nonin Equanox in the OR):** all participants received premedication with oral diazepam (0.1 to 0.2 mg/kg) Upon arrival in the operating room standard monitors were connected, including 5-lead electrocardiogram, pulse oximeter, capnography and radial artery catheter. Prior to induction of anaesthesia, all the participants in both the groups had Nonin Equanox (model 7600) cerebral oximeter sensor in the OR. The interventions for desaturation included the following: repositioning of the head or perfusion cannulae; increasing arterial CO_2 tension; increasing systemic arterial blood pressure; adjusting the pump flow rate; adjusting the anaesthetic depth; reduction of temperature; vasodilatation; increase in haematocrit. "We followed the algorithm proposed... " N = 50 **Control group:** rSO_2 data were collected, but the anaesthetist was blinded to the monitoring data N = 50
Outcomes	Postoperative neurocognitive impairment*: 1week and 3 months postoperation (see notes) Postoperative neurocognitive impairment: MMSE, ASEM, 1week and 3 months postoperation Length of ICU stay Length of extubation (this outcome was not planned in our protocol) - Unable to use: The occurrence of abnormal rSO_2 during or after surgery: desaturation** (see notes): the authors did not report these data The occurrence of abnormal rSO_2 during or after surgery: AUC, skewed data; we present these data as 'other data' in the data analysis section
Notes	Funding source: none Declarations of interest: Quote: "Conflict of Interest: None declared" *A decrease in the MMSE and ASEM scores… (page 104, line 38, left; page 105 table 4). "Postoperative MMSE impairment was defined as a decrease in scores by more than 20% of the preoperative values" (page 103, line 21, right) "Postoperative ASEM impairment was defined as a decrease of scores to more than 30% of preoperative values." (page 103, line 41, right) **"Cerebral desaturation was defined as a decrease in saturation values below 80% of the baseline or an absolute value below 50% for one minute or longer." (page 103, line 40, left) **Contact the author for further information:** 1. Need to contact the author of the original study for more details about randomization, blinding

Mohandas 2013 *(Continued)*

2. Desaturation rate of rSO_2 in each group

3. Statistical tests used for continuous data

4. The person who measured the outcome

Author's contact information:

Correspondence: Dr. Mohandas BS, Department of Cardiac Anesthesia, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bannerghatta Road, Bangalore - 560 069, Karnataka, India

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We contacted Dr. Mohandas by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "100 patients were randomly allocated to...." (page 102, line 3, abstract) Comment: the authors mentioned randomization but did not state the methods; in this case we accepted the authors' reporting as true and accurate
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The extubation and ICU discharge were decided by the intensivists and they were blinded to the interventions carried out in the operating room for increasing the rSO_2" (page 103, line 9, right) Comment: the blinding of other outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Unclear risk	Quote: "... the number of patients experiencing desaturation is not reported in each group." (page 104, table 1 and table 3) Comment: 1 secondary outcome is not reported
Other bias	Low risk	Comment: none obvious

Murkin 2007

Methods	**Design:** 2-arm, parallel RCT **Period:** from September 2002 to April 2004, 20 months **Follow-up:** not reported **Settings:** preoperative clinic, Canada

Murkin 2007 *(Continued)*

Participants	**Total N randomized:** N = 200 **Surgery type:** scheduled for primary elective coronary artery bypass (CAB) surgery with use of cardiopulmonary bypass (CPB) **Age:** mean 61.8 years, SD 9.3 years **Sex:** male 175, female 25 **Bypass time:** mean 88.7 min, SD 38.7 min **Clamp-time:** mean 59.4 min, SD 23.2 min **Inclusion criteria:** Age > 18 years, scheduled for primary elective CAB surgery with use of CPB **Exclusion criteria:** Patients were not routinely preoperatively screened for evidence of carotid artery disease
Interventions	2 study groups: **Intervention group (Invos 5100 in the OR)**: active treatment with cerebral oximetry monitoring using NIRS bilaterally in the OR. A prioritized intraoperative management protocol was used to maintain rSO_2 values at or above 75% of the baseline threshold. Device type: Invos 5100; Somanetics Corporation, Troy, MI N = 100 **Control group**: "...the screen was electronically blinded and continuously recorded after verification of adequate signal strength and baseline values were calculated post hoc by taking the average of data over 1 min, 3 min after beginning recording" N = 100
Outcomes	Postoperative stroke or other neurological injury: new onset stroke, within the first 30 days after surgery Intraoperative mortality or postoperative mortality: mortality, within the first 30 days after surgery The occurrence of abnormal rSO_2 during or after surgery: incidence of prolonged desaturations during surgery*; mean rSO_2, rSO_2< AUC 75%, rSO_2 < AUC 40% Myocardial infarction within the first 30 days after surgery Any major non-neurological complications: cardiac (myocardial infarction, arrhythmia), renal failure requiring dialysis, mediastinitis, septicaemia, wound infection, major organ morbidity and mortality (MOMM) within the first 30 days after surgery Length of ICU stay - Unable to use Readmission: this outcome was not planned in our protocol Length of hospital stay: skewed data; we present these data as 'other data' in the data analysis section
Notes	*An index of the degree and duration of desaturations was determined by examining the incidence of prolonged desaturations where the AUC of rSO_2 values < 70% of baseline was > 150% minutes duration ($AUC_{rSO2 < 70\% \text{ baseline} > 150\% \text{ min}}$) Funding source: Quote: "Supported in part by Canadian Institutes of Health Research grant MOP37914, and a grant from Somanetics Corporation"

Murkin 2007 *(Continued)*

Declarations of interest: Quote: "Dr. Murkin has received lecture/travel fees from neuromonitoring companies, including Somanetics, but has no stock equity, consulting agreements, or other financial interests in Somanetics. None of the other authors have any relevant disclosures."

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by means of sealed opaque envelopes assigning treatment allocation and placed in computer-generated random order which were drawn in sequence as each patient was enrolled in the study and were opened in the OR at the time of surgery." (page 53, line 224-29, right) Comment: the authors gave sufficient information on the generation of randomization
Allocation concealment (selection bias)	Low risk	Quote: "... sealed opaque envelopes assigning treatment allocation..." (page 53, line 25-26, right) Comment: sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patients were anaesthetized during the surgery. Quote: "To maintain postoperative blinding, no study group identifiers were included with the patient or in the patients' charts. Postoperatively, all patients were transferred to an autonomous, protocol-driven, "closed" ICU, under the exclusive care of ICU physicians without direct reference to the attending surgeons or anaesthesiologists" The anaesthesia providers were unlikely to be blind to the treatment condition (page 53, line 41-47, left) Comment: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "... data on perioperative complications were compiled and registered concomitantly by an independent blinded observer using the same variables" (page 53, line 59, left) Comment: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary analysis undertaken was "intent-to-treat" without exclusion of any patients once randomization had occurred." (page 53, line 56-57, right) "Technical failure resulted in loss of rSO_2 data from the floppy discs of six patients, with resultant NIRS data from 194 patients for cerebral rSO_2 analysis." (page 55, line 18-21, left) Comment: only 3% of the participants were missing. The proportion of missing outcomes, compared with observed events, was not large enough to induce important bias in the intervention effect estimate.
Selective reporting (reporting bias)	Low risk	Comment: all prespecified outcomes were reported

Murkin 2007 *(Continued)*

Other bias	High risk	Quote: "Supported in part by Canadian Institutes of Health Research grant MOP37914, and a grant from Somanetics Corporation." (page 51, line 13, left) "Dr. Murkin has received lecture/travel fees from neuro monitoring companies, including Somanetics, but has no stock equity, consulting agreements, or other financial interests in Somanetics." (page 51, line 18, left) Comment: there might be a conflict of interest, but we do not have enough information to determine

Slater 2009

Methods	**Design:** 2-arm, parallel RCT **Period:** from January 2004 to February 2006, 26 months **Follow-up:** of the 240 participants, 202 (84%) had neurocognitive testing at 3 months. The authors did not report the reasons for dropouts. **Settings:** Morristown Memorial and Gagnon Heart Hospital, New Jersey
Participants	**Total N randomized:** N = 240 **Surgery type:** scheduled for primary elective CAB surgery with use of cardiopulmonary bypass (CPB) **Age:** mean 64.33 years, SD 10.2 years **Sex:** male 201, female 39 **Bypass time:** mean 64.90 min, SD 19.1 min **Clamp-time**: mean 39.47 min, SD 13.6 min **Inclusion criteria:** Patients undergoing primary coronary artery bypass grafting using cardiopulmonary bypass **Exclusion criteria:** Pre-existing neuropsychiatric disorders; inability to correctly perform the neurocognitive tests; mini mental state examination score of 23 or less; off-pump coronary artery bypass grafting; unplanned concomitant intraoperative procedures (i.e. patent foramen ovale repair, mitral valve repair) and one 80-year-old male who expired on postoperative day 2
Interventions	2 study groups: **Intervention group (INVOS in the OR)**: participants had INVOS cerebral oximeter sensors placed bilaterally on the forehead During surgery, participants in the intervention group had rSO_2 values displayed on a screen and recorded continuously during the entire procedure. Interventions to treat decreasing rSO_2 included the following: repositioning of the head or perfusion cannulae; increasing arterial carbon dioxide tension, increasing systemic arterial blood pressure, adjusting pump flow rate or anaesthetic depth; reduction of temperature; vasodilation; or blood transfusion. To determine the order of intervention, the value farthest from acceptable range was modified first at the anaesthesiologist's discretion. Interventions were performed only in the operating room. Device type: INVOS 5100BTM; Somanetics Corp, Troy, MI N = 125 **Control group**: rSO_2 was recorded; however, the values were not displayed and no specific treatments were employed to improve cerebral oxygenation

Slater 2009 *(Continued)*

	N = 115
Outcomes	Postoperative cognitive decline* (see notes): prior to discharge and at 3 months postoperatively The occurrence of abnormal $rScO_2$ during surgery: prolonged cerebral desaturation during surgery** (see notes) - Unable to use Postoperative delirium: prior to discharge and at 3 months postoperatively. The authors did not report these data Any major postoperative complications the authors did not report these data Hospital stay: prolonged length of hospital stay*** (see notes). The authors did not report these data.
Notes	*Cognitive decline was defined as a decline of 1standard deviation or more in performance on 1or more of the neuropsychologic tests **The rSO_2 at 50% represents the average of observed intraoperative cerebral oxygen saturations. Prolonged rSO_2 desaturation was defined as rSO_2 score greater than 3000%-second below a 50% saturation threshold ***Length of hospital stay > 6 days Funding source: study funding sources were not reported Declarations of interest: not reported **Contact the author for further information:** 1. The authors presented the data in percentages; the exact numbers are needed (gender; POCD prior to discharge; prolonged cerebral desaturation) 2. Other information is needed: i. The number of participants who did not complete the neurocognitive test at 3 months in the 2 study groups, respectively ii. The POCD and postoperative delirium data in the intervention group and control group, respectively iii. The incidence of "prolonged length of hospital stay" in the intervention group and control group, respectively iv. The incidence of "major postoperative complications" in the intervention group and control group, respectively v. The length of hospital stay (in days) in the intervention group and control group, respectively **Author's contact information:** James P. Slater Mid-Atlantic Surgical Associates, 95 Madison Avenue, Morristown, NJ 07962 Email: james.slater@atlantichealth.org We contacted Dr. James P. Slater by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement

Slater 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was based on a table of random numbers. The first number was blindly chosen, subsequent assignments were sequentially dictated by the table. Even numbered patients were assigned to the intervention group and odd numbers to the control group." (page 37, line 12-16, left) Comment: the authors gave sufficient information on the generation of randomization
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patient was blinded to their group assignment." (page 37, line 16-17, left) Comment: blinding of participants was ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 240 patients, 202 (84%) had neurocognitive testing at 3 months." (page 41, line 14-15, right) Comment: the attrition rate was 16% and the authors did not report the reasons for dropouts
Selective reporting (reporting bias)	Low risk	Comment: all prespecified outcomes were reported
Other bias	Low risk	Comment: no obvious risk of bias

Trafidlo 2015

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Follow-up:** not reported **Settings:** Clinical Department of Neurosurgery and Oncology of the Central Nervous System, Medical University of Lodz, Poland
Participants	**Total N randomized:** N = 43 **Surgery type:** lumbar spine surgery **Age:** mean (95% CI), intervention group: 50.58 (40.32 to 60.84) years; control group: 49.22 (44.12 to 54.32) years **Sex:** unclear **Duration of surgery:** unclear **Inclusion criteria:** adult patients who qualified for surgical treatment of lumbar spondylosis in the Clinical Department of Neurosurgery and Oncology of the Central Nervous System, Medical University of Lodz, Poland in 2012 **Exclusion criteria:** patients with a history of neurological and psychiatric disorders which impair cognitive processes were disqualified from the study. These include previously established dementia, stroke, schizophrenia and depression. Individuals undergoing or with a history of treatment with hypnotics, antidepressants, anxiolytics and steroids were also excluded from the study. Also those who re-

Trafidlo 2015 *(Continued)*

	ported frequent alcohol consumption (above 50 g per day) and whose preoperative laboratory tests showed elevated GGT (gamma-glutamyl transpeptidase) and macrocytosis with hyperchromia were disqualified
Interventions	2 arms: **Intervention group (INVOS in the OR):** monitored intraoperatively by means of NIRS cerebral oximetry (INVOS 5100, Somanetics Corporation, USA). A downward tendency of $ScrO_2$ oximetry index (cerebral regional oxygen saturation) by more than 20% from the baseline may be a manifestation of a significant tissue hypoxia. The measured values of $ScrO_2$ at the output in INVOS 5100 most frequently oscillated above 70 units. They focused mainly on improving the head positioning whenever $ScrO_2$ declined by 20% from the baseline. When systemic pulse oximetry saturation (SpO_2) declines were noted, observers improved the orientation of the pulse oximeter sensor. If this intervention was not effective the increase of FiO_2 took place. Device type: Somanetics Invos Cerebral Oximeter (SICO, Covidien inc, Co, USA) N = 13 **Control group:** without NIRS monitoring N = 30
Outcomes	Episodes of $ScrO_2$ reduction Duration of episodes of $ScrO_2$ reduction Cognitive test: N-back Test (NBT), Digit Span Test (DST) Adverse events
Notes	Trial registration: RNN/556/08/KBe approval of the ethics committee at Medical University of Lodz, Poland Funding source: granted by Medical University of Lodz. Project number: 502-03/7-128-03/502-54-004. No significant financial support for this work that could have influenced its outcome. Declarations of interest: Quote: "The authors declare that there are no known conflicts of interest associated with this publication" **Author's contact information:** Corresponding author: K. Nowakowska-Domagała Email: tamara.trafidlo@umed.lodz.pl (T. Trafidło), tomasz.gaszynski@umed.lodz.pl (T. Gaszynski), wojciech.gaszynski@umed.lodz.pl (W. Gaszynski), katarzyna.nowakowska@umed.lodz.pl (K. Nowakowska-Domagała) We contacted Dr. K. Nowakowska-Domagała by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the procedures the patients were randomized into two subgroups..." (page 24) Comment: there was no further description of randomization methods, but we accepted the authors' reporting as true and accurate

Trafidlo 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided about blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: observers were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data
Selective reporting (reporting bias)	High risk	Comment: all prespecified outcomes were reported, but the numbers of patients in the DST and NBT tests were different from the randomized numbers
Other bias	Low risk	Comment: none obvious

Vretzakis 2013

Methods	**Design:** 2-group, parallel RCT **Period:** over 16 months, but dates were not reported **Follow-up:** not reported **Settings:** in a tertiary care university hospital
Participants	**Total N randomized:** 150 (sample size calculation was reported) **Age:** 67.3 ± 8.5 (intervention group), 65.9 ± 9.5 (control group) **Sex:** male/female, 63/12 (intervention group), 60/15 (control group) **Cardiopulmonary bypass time:** 88.8 ± 18.2 min (intervention group), 93.7 ± 29.8 min (control group) **Operation time:** 249.9 ± 41.9 min (intervention group), 248.0 ± 59.2 min (control group) **Country:** USA **Inclusion criteria:** patients undergoing elective cardiac surgery under cardiopulmonary bypass, with no age or ASA physical status classification limit **Exclusion criteria:** patients undergoing emergency or re-do operations, combined cardiac-carotid surgery and operations with minimal extracorporeal flow (surgery of the ascending aorta) or circulatory arrest; patients with haematologic disease (including anaemia requiring preoperative blood product transfusion), coagulation abnormality, advanced cirrhosis and renal dysfunction (creatinine > 50% upper limit of normal value)
Interventions	2 study groups: **Intervention group (INVOS group in the OR):** "In group A (INVOS), decisions were as follows: If mean INVOS value from both hemispheres was less than 60 regardless of baseline values, (criterion a) or INVOS decreased by 20% or more compared to the mean value during pulmonary artery catheter insertion (criterion b), the patient was candidate for transfusion, but was transfused only if hematocrit from the arterial blood-gas analysis was indicating the need for transfusion (see below: indications in group B). Patients with low hematocrit values who did not meet the INVOS criteria (a or b, as described above) did not receive blood transfusions"

Vretzakis 2013 *(Continued)*

	Device type: INVOS 5100 device (Somanetics, USA) N = 75 **Control group (without INVOS monitoring):** "In group B (control group, no INVOS) transfusion decisions were based on hematocrit-based rules as follows: During aortic cross-clamp, allogeneic blood was not given if hematocrit was > 21%. For values ≤17%, one unit of RBC was transfused. When hematocrit was between 17-21%, anaesthesiologists could decide based on their clinical judgment. After aortic clamp removal and before weaning from CPB (usually near the completion of the last proximal anastomosis or during cardiac reperfusion), RBCs were transfused for hematocrit less than 21%. After weaning from CPB and re-transfusion of salvaged blood, patients were transfused for hematocrit ≤24%" N = 75
Outcomes	Postoperative mortality within 30 days of discharge from the hospital Postoperative complications ("defined as events that required some specific acute medical therapy or intervention resulting in prolonged (>9 days) hospital stay or death") Length of ICU stay Length of hospital stay
Notes	1centre (a tertiary care university hospital) Funding source: Quote: "supported solely by department funds" Declarations of interest: Quote: "All authors declare they have no conflict of interest to report" Corresponding author: Menelaos Karanikolas Address: Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110, USA Email: kmenelaos@yahoo.com Trial registration: ClinicalTrials.gov NCT00879463

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment originated from a sequentially numbered sealed envelope containing a randomization code" Comment: randomization was implied
Allocation concealment (selection bias)	Low risk	Quote: "Group assignment originated from a sequentially numbered sealed envelope containing a randomization code" Comment: numbered and sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All personnel (including the surgical team, perfusionist, nursing and ICU personnel) involved in the care of these patients were blinded to group assignment." "However, the anaesthesiologist in charge of each case had access to the INVOS data and, obviously, was not blinded" Comment: we feel that an adequate level of blinding was applied

Vretzakis 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…all investigators who collected data were also blinded."... "Data were collected by blinded investigators…" Comment: blinded assessment was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In total, 150 patients were enrolled, and there were no cases of missing data." Comment: no missing data
Selective reporting (reporting bias)	Low risk	Comment: all prespecified outcomes were reported
Other bias	Low risk	Comment: none obvious

Zogogiannis 2011

Methods	**Design:** 2-arm, parallel RCT **Period:** from December 2007 to January 2010, 25 months **Follow-up:** not reported **Settings:** 2 Greek institutions, Greece
Participants	**Total N randomized:** N = 253 **Surgery type:** carotid endarterectomy (CEA) **Age:** mean ˜69.1 years, range: 48 to 82 years **Sex:** male 185, female 68 **Operation time**: not reported **Inclusion criteria:** Patients were American Society of Anesthesiologists physical status II-III, aged 42 to 82 years who underwent carotid endarterectomy **Exclusion criteria:** not reported
Interventions	2 study groups: **Group A (INVOS in the OR group):** standard monitoring in all participants included electrocardiography (ECG), end tidal carbon dioxide ($EtCO_2$), invasive blood pressure (IBP) and pulse oximetry (SpO_2). In addition to the above mentioned monitoring, cerebral oximetry with near-infrared refracted spectroscopy was used. participants in group A were managed according to the algorithm developed by Denault et al for participants undergoing cardiac surgery. Device type: INVOS 4100, Somanetics Inc., Troy MI N = 83 **Group B (INVOS in the OR group):** standard monitoring in all participants included ECG, $EtCO_2$, IBP and SpO_2. In addition to the above mentioned monitoring, cerebral oximetry with near-infrared refracted spectroscopy was used. Cerebral oximetry values were recorded but anaesthesia management was not based on the aforementioned algorithm. Device type: INVOS 4100, Somanetics Inc., Troy MI N = 84

Zogogiannis 2011 *(Continued)*

	Group C (control group, without INVOS monitoring): participants in the third group (Group C) underwent routine CEA without INVOS monitoring and served as the control group. N = 86
Outcomes	Postoperative stroke or other neurological injury: neurologic deficits* (see notes) Any major non-neurological complications: cardiac ischaemia - Unable to use The occurrence of abnormal $rScO_2$ during or after surgery: odds of rSO_2; the data for the control group were not available
Notes	Funding source: not reported Declarations of interest: Quote: "We have not received financial support (reimbursements, fees, funding, or grants) from an organization that may in any way gain or lose financially from the publication of this manuscript. We do not have any other financial competing interests" *Participants who exhibited new neurological deficits postoperatively that persisted for more than 24 hours underwent a follow-up brain computed tomography (CT) scan; we used the data from group A to perform aggregation but not group B Need to contact the author: the method of blinding **Author's contact information:** Vassilios K Dimitriou, Associate Professor of Anesthesia, Head of Department of Anesthesia, "G Gennimatas" General Hospital of Athens, 154 Mesogion Avenue, 11527 Athens, Greece. Fax: +302132032212 Email address: vaskdimi@otenet.gr We contacted Dr. Vassilios K Dimitriou by email to request detailed information for the study, but we did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated by using closed envelopes into three groups" (page 368, line 26, right) Comment: the authors did not describe the method of randomization, however we accepted the authors' reporting as true and accurate
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated by using closed envelopes into three groups" (page 368, line 26, right) Comment: allocation concealment was done via closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was insufficient information about blinding of outcome assessment

Zogogiannis 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "2 out of the total 253 patients (0.8%), one in group B and one in group C, expired due to cardiovascular events, postoperatively" (page 371, line 23, left) Comment: the proportion of missing outcomes, compared with observed events, was not large enough to induce important bias in the intervention effect estimate
Selective reporting (reporting bias)	Low risk	Comment: all the prespecified outcomes were reported
Other bias	Unclear risk	Comment: none obvious

AF: atrial fibrillation; ASA: American Society of Anesthesiologists; ASEM: antisaccadic eye movement test; AUC: area under curve; BIS: bispectral index; BP: blood pressure; CABG: coronary artery bypass grafting; CI: confidence interval; CO_2: carbon dioxide; CPB: cardiopulmonary bypass; CT: computed tomography; DHCA: deep hypothermic circulatory arrest; DST: Digit Span Test; ECG: electrocardiography; epid: epidural; $EtCO_2$: end tidal carbon dioxide; FiO_2: fraction of inspired oxygen; g: gram; $g.dl^{-1}$: gram per decilitre; GGT: gamma-glutamyl transpeptidase; Hb: haemoglobin; Hct: haematocrit; HDU: high dependency unit; HIV: human immunodeficiency virus; IBP: invasive blood pressure; ICU: intensive care unit; INVOS: one trademark of cerebral oximetry; IV: intravenous injection; Kg: kilogram; mg: milligram; min: minute; MOMM: major organ morbidity and mortality; mmHg: millimetres of mercury; MMSE: mini-mental state examination; N: number; NBT: N-back Test; NIHR: the National Institute for Health Research; NIRS: near-infrared spectroscopy; NYHA: New York Heart Association; OR: operating room; pCO_2: partial pressure of carbon dioxide; POCD: postoperative cognitive dysfunction; POD: postoperative delirium; PRBC: packed red blood cells; RBC: red blood cell; RCP: retrograde cerebral perfusion; RCT: randomized controlled trial; rSO_2: regional cerebral oxygen saturation; S100: one biomarker of cerebral damage; $ScrO_2$: local saturation of the cerebral cortex; SD: standard deviation; SICO: Somanetics Invos Cerebral Oximeter; SpO_2: pulse oximetry saturation; TIA: transient ischaemic attack; vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kussman 2009	This was a cohort study that was part of a RCT comparing early postoperative and neurodevelopmental outcomes after haemodilution to a haematocrit of 25% versus 35% during infant heart surgery. The authors failed to demonstrate a relationship between intraoperative cerebral oxygen saturation and early postoperative outcomes.
Kussman 2010	This was a secondary analysis of data arising from a RCT of haemodilution to a haematocrit of 25% versus 35% during cardiopulmonary bypass in infants. The authors evaluated the correlation between intraoperative cerebral oxygen saturation and postoperative neurological outcomes at the age of 1 year.
Murkin 2011	This was a post hoc analysis of a subset of participants in another RCT (Murkin 2007) and focused on patients with a preoperative diagnosis of diabetes mellitus.

RCT: randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Aguirre 2016

Methods	**Design:** 2-arm, prospective study **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported

Aguirre 2016 *(Continued)*

	Withdrawals: not reported **Follow-up:** not reported **Settings:** not reported
Participants	**Total N randomized:** N = 80 **Surgery type:** elective shoulder surgery **Age:** not reported **Sex:** not reported **Duration of surgery:** not reported **Inclusion criteria:** ASA II-IV patients scheduled for elective shoulder surgery **Exclusion criteria:** not reported
Interventions	2 arms: **Intervention group:** "intravenous general anaesthesia group using a NIRS-based protocol" **Control group:** "assessor-blinded study according to clinical standard into a regional anaesthesia"
Outcomes	Postoperative cognitive function Intraoperative cerebral desaturation events
Notes	This is an abstract for a study; a full text is required, but there is no contact information for the corresponding author We tried to contact the relevant research group through their institutions and acquired Dr. Aguirre's email address (jose.aguirre@balgrist.ch). Dr. Aguirre replied that a preliminary report will be submitted shortly (not all parts were included)

Baker 2006

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported **Withdrawals:** not reported **Follow-up:** not reported **Settings:** not reported
Participants	**Total N randomized:** N = 97 **Surgery type:** patients undergoing primary coronary artery bypass grafting using cardiopulmonary bypass **Age:** not reported **Sex:** not reported **Duration of surgery:** not reported **Inclusion criteria:** not reported

Baker 2006 *(Continued)*

	Exclusion criteria: not reported
Interventions	2 arms: **Intervention group:** not reported N = 45 Device type: Somanetics Invos Cerebral Oximeter (SICO, Covidien inc, Co, USA) **Control group:** not reported N = 42
Outcomes	- Unable to use* ICU length of stay: median and IQR were reported; we will present these data as 'other data' in the data analysis section Hospital length of stay: median and IQR were reported; we will present these data as 'other data' in the data analysis section
Notes	This is an abstract for a study: a full text is required, but there is no contact information for the corresponding author We tried to contact the relevant research group through their institutions and acquired Dr. Baker's email address (Rob.Baker@flinders.edu.au). We have not yet received a reply.

Ellis 2015

Methods	**Design:** multicentre, 2-arm, parallel RCT **Period:** over a 5-year period **Generation of allocation:** randomized in blocks of varying size in a 1:1 ratio, stratified by centre and planned surgery; allocations are generated by computer in advance of starting recruitment **Allocation concealment:** concealed using an Internet-based system; sealed envelopes **Withdrawals:** not reported **Follow-up:** follow-up on all study participants was completed in April 2014 **Settings:** Bristol Royal Infirmary in Bristol, Glenfield Hospital in Leicester and Castle Hill Hospital in Hull
Participants	**Participants:** aged over 16 years **Total N randomized:** N = 200 participants (100 per group) **Surgery type:** nonemergency valve or combined coronary artery bypass graft (CABG) and valve surgery using cardiopulmonary bypass (CPB) at mild hypothermia (32°C to 35°C) **Age:** not reported **Sex:** not reported **Inclusion criteria:** adult (≥ 16 years) cardiac surgical patients undergoing nonemergency valve or combined CABG and valve surgery using CPB at the Bristol Royal Infirmary in Bristol, Glenfield Hospital in Leicester, or Castle Hill Hospital in Hull; given informed consent **Exclusion criteria:** patients undergoing emergency cardiac surgery; patients who are prevented from having blood and blood products according to a system of beliefs; patients who may have

Ellis 2015 *(Continued)*

	higher perioperative haemoglobin requirements or critical limb ischaemia; patients with congenital or acquired RBC, platelet, or clotting factor disorders; patients with a neurological disorder; patients with a diagnosed psychiatric disorder, drug, or alcohol addiction; patients with an already identified cognitive impairment as defined by psychometric assessment or a preoperative Mini Mental State Examination score of < 24; patients who have previously sustained a stroke, intracerebral haemorrhage, or acquired brain injury; patients with a pre-existing inflammatory state; patients with end-stage renal failure or patients who have undergone renal transplantation; patients unable to complete the cognitive assessments required for the trial (e.g., due to language difficulties, visual, or hearing impairment); patients who are unable to give full informed consent for the study; patients already participating in another clinical (interventional) study
Interventions	2 arms: **Intervention group:** "Patient-specific algorithm" (including a restrictive transfusion threshold): patient-specific, goal-directed algorithm based on the monitoring and optimization of regional cerebral oxygen saturation, combined with a predefined restrictive intraoperative haematocrit transfusion threshold of 18 Target regional oxygen saturation values are specified as 70% or more of pre-induction values and an absolute value of 50% or more. However, if the regional oxygen saturation remains at or above these target values, but the haematocrit falls to 18, then RBC transfusion is indicated Device type: INVOS 5100 (Somanetics, Troy, MI, USA) **Control group:** "Generic algorithm" (including a standard transfusion threshold): based on global measures of oxygen utilization and including a predefined intraoperative haematocrit transfusion threshold of 23
Outcomes	Primary outcome: cognitive function measured at 3 months after surgery Secondary outcome: units of RBC and other blood components transfused during the operative period and postoperative hospital stay; cerebral oxygenation during the operative period; oxygen delivery and utilization during CPB; EuroQol EQ-5D-3L (a generic health-related quality of life instrument that measures mobility, self-care, usual care, pain/discomfort and anxiety/depression) assessed at baseline and at 6 weeks and 3 months after surgery; length of CICU or high dependency unit (HDU) stay; length of postoperative hospital stay; clinical outcomes defined as infectious complications (sepsis and wound infection), stroke (validated by CT scanning), ST elevation myocardial infarction accompanied by troponin >5 ng/mL, postoperative acute kidney injury (defined as AKIN criteria stage 1, 2, or 3), and respiratory complications (i.e. reintubation, ventilation > 48 hours, tracheostomy, or acute respiratory distress syndrome); sepsis; stroke; cumulative resource use, cost and cost-effectiveness; all-cause mortality within 30 days of surgery; biochemical markers of organ injury
Notes	**Funding source:** sponsored by NIHR (Grant Reference Number RP-PG-0407-10384) and the University Hospitals Bristol NHS Foundation Trust **Declarations of interest:** none declared **Author contact details:** Chris A Rogers, PhD Clinical Trials & Evaluation Unit, University of Bristol, Level 7 Queen's Building, Bristol Royal Infirmary, Bristol, BS2 8HW, United Kingdom Phone: 44 (0)117 342 2507 Fax: 44 (0)117 342 3288 Email: chris.rogers@bristol.ac.uk Trial registration: http://www.isrctn.com/ISRCTN23557269 This is the protocol for a RCT and the results are to be published (early 2016)

Ellis 2015 *(Continued)*

	We tried to contact the corresponding author, but have not yet received a reply

Gauge 2014

Methods	**Design**: 2-arm, parallel RCT **Period:** no more details in the abstract **Generation of allocation:** no more details in the abstract **Allocation concealment:** no more details in the abstract **Withdrawals:** no more details in the abstract **Follow-up:** no more details in the abstract **Settings:** no more details in the abstract
Participants	**Participants:** aged over 64 years **Total N randomized:** N = 81 **Surgery type:** coronary artery bypass graft surgery **Age:** mean age ˜71.9 years **Sex:** male 70, female 11 **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	2 study groups: **Intervention group:** "aimed at a BiSpectral Index (BIS) of 50 ± 10 and standardized interventions were delivered if cerebral oxygenation (rSO_2) dropped below 15% of the baseline or below 50%" N = unclear **Control group:** "blinded to BIS and rSO_2" N = unclear
Outcomes	Postoperative delirium at 3 ± 1 days after surgery using the Confusion Assessment Method (CAM)
Notes	We need the full text for this study, but there is no contact information for the corresponding author We tried to contact the relevant research group through their institutions and acquired Dr. Gudrun Kunst's email address (gudrun.kunst@kcl.ac.uk). We have not yet received a reply.

Girgin 2012

Methods	**Design**: 2-arm, parallel RCT **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported

Girgin 2012 *(Continued)*

	Withdrawals: not reported **Follow-up:** not reported **Settings:** not reported
Participants	**Total N randomized:** N = 100 **Surgery type:** coronary artery bypass grafting (CABG) **Age:** not reported **Sex:** not reported **Duration of surgery:** not reported **Inclusion criteria:** patients between 18 and 65 years of age undergoing coronary artery bypass grafting (CABG) **Exclusion criteria:** not reported
Interventions	2 arms: **Intervention group:** when a 20% decrease from baseline NIRS monitor was detected, a predefined intervention algorithm was used to treat desaturation **Control group:** "without any evidence of NIRS values, management was maintained in accordance with clinical practice and experience"
Outcomes	Postoperative neurocognitive function ICU length of stay Duration of total hospitalization
Notes	We need the full text for this study, but there is no contact information for the corresponding author We tried to contact the relevant research group through their institutions and acquired Dr. Murat Aksun's email address (murataksun@yahoo.com). We have not yet received a reply.

Hosang 2017

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported **Withdrawals:** not reported **Follow-up:** not reported **Settings:** Otto-von-Guericke-Universität Magdeburg
Participants	**Total N randomized:** N = 10 **Surgery type:** coronary artery bypass grafting (CABG) **Age:** median age was 68 (62 to 77) years **Sex:** male 8, female 2 **Duration of surgery:** not reported

Hosang 2017 *(Continued)*

	Inclusion criteria: patients undergoing CABG at high risk of cerebrovascular events **Exclusion criteria:** patients with symptomatic carotid stenosis and/or previous cerebral infarctions
Interventions	2 arms: **Intervention group:** "Received intraoperative frontal regional cerebral-tissue oxygenation (rSO_2) monitoring as well as appropriate measures to optimize rSO_2 in case of desaturations" N = 5 **Control group:** no more details in the abstract N = 5
Outcomes	Cognitive function on postoperative days 5 to 7, using the Montreal Cognitive Assessment (MoCA), Trail-making Test (TMT A/B), Regensburg Word Fluency Test (RWT) and the Boston Naming Test (BNT) The rSO_2 area under the curve (desaturations below 50% * time (min), mean value of left and right frontal channel) Length of hospital stay
Notes	This is a report of the preliminary results of an ongoing prospective study. We need to find the full text for this study. However, there is no contact information for the author.

Iglesias 2003

Methods	**Design:** 2-arm, parallel RCT **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported **Withdrawals:** not reported **Follow-up:** not reported **Settings:** not reported
Participants	**Total N randomized:** N = 98 **Surgery type:** coronary artery bypass (CAB) surgery **Age:** not reported **Sex:** not reported **Duration of surgery:** not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	2 arms: **Intervention group:** regional cerebral oxygen saturation (rSO_2) "... was visible and efforts to keep the rSO_2 on levels ≥ 75% of preinduction value by sequentially increasing perfusion pressure, pump

Iglesias 2003 *(Continued)*

	flow, $PaCO_2$ (if < 35 mmHg), FiO_2, decrease temperature (if > 37°C), increase $PaCO_2$ > 45 mmHg, increase Hct (if < 20%)" N = 44 **Control group:** "... the monitor was covered and the patient was managed routinely" N = 54
Outcomes	Neurological complications Length of stay (LOS)
Notes	We need to find the full text for this study. However, there is no contact information for the author. We tried to contact the relevant research group through their institutions and acquired Dr. Iglesias's email address (iglesias@uwo.ca). We have not yet received a reply.

Lei 2017

Methods	**Design:** 2-arm, parallel RCT **Period:** from January 2012 to April 2015 **Generation of allocation:** computer-generated randomization code in blocks of 4, aiming at participant allocation in a 1:1 ratio **Allocation concealment:** not reported **Withdrawals:** 1 patient from the intervention group died in the operating room **Follow-up:** not reported **Settings:** a single-centre study in the quaternary referral hospital in Toronto, Canada
Participants	**Total N randomized:** N = 250 (a total of 250 patients were randomly allocated, and 249 analysed. 1 patient from the intervention group died in the operating room) **Surgery type:** cardiac surgery with cardiopulmonary bypass **Age:** mean 74.2 years, SD 6.5 years (intervention group), mean 72.9 years, SD 6.3 years (control group) **Sex:** male 88/female 35 (intervention group), male 88/female 38 (control group) **Duration of surgery:** not reported **Inclusion criteria:** patients ≥ 60 years of age, undergoing combined valve and coronary revascularization procedures, repeat cardiac surgery, multiple valve replacement or repair, or surgery of ascending aorta and aortic arch, with or without circulatory arrest **Exclusion criteria:** patients with a history of serious mental illness, delirium or who were planned to undergo either emergency or surgery without bypass
Interventions	2 arms: **Intervention group:** "Bilateral NIRS sensors (INVOSTM 5100C; Covidien) were used to measure rSc02 intra-operatively and postoperatively, up to 24 h in ICU" "an algorithm was commenced if regional cerebral oxygen saturation decreased below 75% of baseline value for 1 min or longer" N = 124

Lei 2017 *(Continued)*

	Control group:"the cerebral oximetry monitor screen was electronically blinded" N = 126
Outcomes	Postoperative delirium for the first 7 postoperative days or until discharge (at 12-hour intervals), using the confusion assessment method for ICU (CAM-ICU) or confusion assessment method (CAM) Major adverse outcomes Duration of ICU and hospital length of stay All-cause in-hospital mortality
Notes	Correspondence author: G. Djaiani Email: george.djaiani@uhn.ca

Rogers 2017

Methods	**Design:** 2-arm, parallel RCT **Period:** between December 2009 and January 2014 **Generation of allocation:** blocked allocations with varying block sizes, generated by computer **Allocation concealment:** concealed using a secure password-protected internet-based randomization system **Withdrawals:** 3 patients withdrew and 1 patient died before surgery in the intervention group; of the 204 randomized patients, 194 were eligible for follow-up at 3 months, and 175 completed the 3-month questionnaire and attended for the neurocognitive assessment **Follow-up:** 3 months after randomization **Settings:** 3 cardiac surgery centres in the UK
Participants	**Total N randomized:** N = 208 **Surgery type:** open valve or combined CABG and open valve surgery **Age:** 65.9 (18.5 to 86.6) years (intervention group), 70.0 (29.5 to 88.7) years (control group) **Sex:** male 66/female 32 (intervention group), male 74/female 32 (control group) **Duration of surgery:** not reported **Inclusion criteria:** adult patients undergoing open valve or combined CABG and open valve surgery scored >= 24 on the Mini Mental State Examination (indicating no cognitive impairment) **Exclusion criteria:** patients with pre-existing neurological disease or inflammatory states
Interventions	4 patients withdrew before surgery. The analysis population therefore comprised 204 participants, 106 of whom were allocated to the control group and 98 to the intervention group 2 arms: **Intervention group:** "This was a patient-specific, goal-directed algorithm based on the monitoring and optimization of regional cerebral oxygen saturation measured using the INVOS 5000 NIRS device (Somanetics, IN, USA), combined with a predefined 'restrictive' intraoperative haematocrit transfusion threshold of 18%. Optimization of cerebral oxygenation used a modified Murkin protocol (see Supplementary Table S2) that aimed to maintain INVOS values at an absolute value of >50% or at >70% of baseline values obtained in the anaesthetic room before induction whilst breathing room air. If target cerebral oxygenation values were not achieved by modifying aspects of pump flow, gas exchange, or depth of anaesthesia as specified in the algorithm, red cells could be transfused above the 18% haematocrit threshold"

Rogers 2017 *(Continued)*

	N = 102 **Control group:**"This was a generic algorithm for optimizing tissue oxygenation based on global measures of oxygen utilization and including a predefined intraoperative haematocrit transfusion threshold of 23%" N = 106
Outcomes	Cognitive function on or between 4 and 7 days after surgery and again at 3 months Biomarkers of the inflammatory response (serum interleukin (IL)-6, IL-8), brain (serum S100) and myocardial (serum troponin) injury Kidney injury (serum creatinine and calculated creatinine clearance, and urine biomarkers of inflammation (neutrophil gelatinase associated lipocalcin (NGAL), liver-fatty acid binding protein (L-FAB)) and tubular epithelial injury (kidney injury molecule-1 and IL-18)) Clinical outcomes, resource use and quality of life
Notes	Funding: National Institute for Health Research (NIHR) Programme Grants for Applied Research (grant HTA: RP-PG-0407-10384 for The PASPORT Trial); Leicester and Bristol NIHR Cardiovascular Biomedical Research Units (The PASPORT Trial); British Heart Foundation (RG/13/6/29947 and CH/12/1/29419 to G.J.M.) Clinical trial registration. http://www.controlled-trials.com, ISRCTN 23557269 Corresponding author: GJ Murphy Email: gjm19@le.ac.uk

Sahan 2014

Methods	**Design:** 2-arm, parallel RCT **Period:** no more details in the abstract **Generation of allocation:** no more details in the abstract **Allocation concealment:** no more details in the abstract **Withdrawals:** no more details in the abstract **Follow-up:** no more details in the abstract **Settings:** no more details in the abstract
Participants	**Participants:** aged over 60 years **Total N randomized:** N = 38 N randomized to intervention group: 17 N randomized to control group: 21 **Surgery type:** elective coronary artery bypass graft surgery **Age:** no more details in the abstract **Sex:** no more details in the abstract **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	2 study groups:

Sahan 2014 *(Continued)*

	Intervention group: "handled according to NIRS values" N = 17 Control group: "treated under conventional monitoring modalities (blood pressures, SpO_2, etc.)" N = 21
Outcomes	Postoperative cognitive dysfunction (POCD) at 1 week and 3 months after surgery
Notes	We need the full text for this study, but there is no contact information for the corresponding author We tried to contact the relevant research group through their institutions and acquired Dr. Emre Camci's email address (ecamci@ttnet.net.tr). We have not yet received a reply.

Trinh 2016

Methods	**Design**: 2-arm, parallel RCT **Period:** not reported **Generation of allocation:** not reported **Allocation concealment:** not reported **Withdrawals:** a cognitive function test was performed in 92 and 78 participants postoperatively at 3 and 6 months, respectively **Follow-up:** 6 months **Settings:** not reported
Participants	**Total N randomized:** N = 125 **Surgery type:** elective cardiac surgery requiring cardiopulmonary bypass (CPB) **Age:** no more details in the abstract **Sex:** no more details in the abstract **Duration of surgery:** 296 (263to 345) min in the intervention group; 308 (258 to 371) min in the control group **Inclusion criteria:** adult patients (> 18 years) who underwent elective cardiac surgery requiring CPB **Exclusion criteria:** patients with severe preoperative cognitive impairment or end-stage organ failure
Interventions	2 study groups: **Intervention group:** an intervention algorithm was used to improve regional cerebral tissue oxygen saturation ($SctO_2$) if desaturation occurred < 60 for > 1 min at either probe N = 59 **Control group:** the $SctO_2$ data were hidden from the perioperative team, unless a critical low value, $SctO_2$ < 40 for > 1 min triggered an alarm N = 66

Trinh 2016 *(Continued)*

Outcomes	Postoperative cognitive function (at 3 and 6 months) Intraoperative desaturation
Notes	This is an abstract for a study. We need the full text of this report. However, there is no contact information provided. We tried to contact the relevant research group through their institutions and acquired Dr. David L Reich's email address (david.reich@mountsinai.org). We have not yet received a reply.

Verborgh 2009

Methods	**Design:** 2-arm, parallel RCT **Period:** no more details in the abstract **Generation of allocation:** randomized; no more details in the abstract **Allocation concealment:** no more details in the abstract **Withdrawals:** no more details in the abstract **Follow-up:** no more details in the abstract **Settings:** no more details in the abstract
Participants	**Total N randomized:** N = 44 **Surgery type:** off-pump coronary artery bypass grafting (CABG) **Age:** no more details in the abstract **Sex:** no more details in the abstract **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	2 study groups: **Intervention group:** regional cerebral oxygen saturation (SrO_2) was actively monitored and not allowed to decrease more than 20% N = unclear Device type: Invos **Control group:** the anaesthesiologist and surgeon were blinded to the values of the SrO_2 N = unclear
Outcomes	- Unable to use Desaturation of regional cerebral oxygen saturation (SrO_2): the authors did not report the data Length of ICU stay: mean and standard deviation were reported, but the authors did not report the number of participants in each group Length of hospitalization: mean and standard deviation were reported, but the authors did not report the number of participants in each group
Notes	We need the full text of this report. However, there is no contact information provided.

Verborgh 2009 *(Continued)*	
	We tried to contact the relevant research group through their institutions and acquired the email address of the Anaesthesiology Department (anesthesie@uzbrussel.be). We have not yet received a reply.

BIS: bispectral index; CAM: confusion assessment method; CABG: coronary artery bypass grafting; Hct: haematocrit; ICU: intensive care unit; IQR: interquartile range; mmHg: millimetres of mercury; N: number; NIRS: near-infrared spectroscopy; $PaCO_2$: partial pressure of carbon dioxide; POCD: postoperative cognitive dysfunction; RCT: randomized controlled trial; rSO_2: regional cerebral oxygen saturation; SrO_2: regional cerebral oxygen saturation; vs: versus

Characteristics of ongoing studies *[ordered by study ID]*

Bal 2016

Trial name or title	Prospective evaluation of cognitive outcomes after anaesthesia on patients in the beach chair position (BCP)
Methods	Randomized, parallel-group, controlled trial (double-blind)
Participants	Enrollment: 90 Inclusion criteria: 18 to 75 years of age; elective shoulder surgery in the beach chair position Exclusion criteria: less than 18 years of age; preoperative score of 23 or less on the pre-operative Mini Mental State Exam; traumatic brain injury; transient ischaemic attack; cerebrovascular incident; any apparent clinical neurologic dysfunction; carotid artery stenosis; known vascular malformation in head; inability to have blood pressure measured in the opposite extremity; malignant hyperthermia
Interventions	Intervention group: anaesthesiologist treats based on near-infrared spectroscopy (NIRS); NIRS monitor allows anaesthesiologist to treat cerebral desaturations according to NIRS results while maintaining mean arterial pressure (MAP) at least 60 mmHg or at least 80% of baseline Control group: anaesthesiologist blinded to NIRS
Outcomes	Primary outcomes: number of cerebral desaturation events; cerebral desaturation event while undergoing elective ambulatory surgery in the beach chair position Secondary outcomes: cognitive decline measured by a drop in Mini Mental State Exam (MMSE) > 2 or a score of 23 (up to 2 weeks)
Starting date	October 2012
Contact information	George K Bal, MD, West Virginia University, Morgantown, West Virginia, United States, 26506-9196
Notes	ClinicalTrials.gov identifier: NCT02674334 Recruiting status: completed https://clinicaltrials.gov/ct2/show/study/NCT02674334 We failed to contact Dr. George K Bal because the email address was not available

Djaiani 2012

Trial name or title	Role of cerebral oximetry in reducing delirium after complex cardiac surgery
Methods	Randomized, parallel-group, controlled trial (double-blind)

Djaiani 2012 *(Continued)*

Participants	Inclusion criteria: adults > 60 years; combined valve and CABG; repeat cardiac surgery; multiple valve replacement or repair; surgery of ascending aorta and aortic arch; signed informed consent Exclusion criteria: cardiac surgery without the use of cardiopulmonary bypass; symptomatic cerebrovascular disease; history of delirium; schizophrenia Estimated enrolment: 266
Interventions	Intervention group: cerebral oximetry monitoring (the INVOS® Cerebral/Somatic Oximeter) intraoperatively and during the 24-hour postoperative period in the ICU; if the threshold of < 75% from baseline rSO_2 value is reached for > 1 minute an algorithm geared to restore rSO_2 to baseline levels will be implemented Control group: "NIRS monitor screen will be electronically blinded"
Outcomes	Primary outcomes: number of participants who suffer from delirium postoperatively assessed postoperatively for 7 days or until discharge
Starting date	December 2011
Contact information	George Djaiani, MD, University Health Network, Toronto General Hospital, Toronto, Ontario, Canada, M5G 2C4 Tel: 416-340-4800 ext 6205 Email address: george.djaiani@uhn.ca
Notes	ClinicalTrials.gov identifier: NCT01707446 Recruiting status: this study is ongoing, but not recruiting participants http://clinicaltrials.gov/ct2/show/study/NCT01707446 We sent an email to Dr. George Djaiani to check if this ongoing study was included in the Deschamps 2016 multicentre trial. The reply was that this study was not included in Deschamps 2016. We contacted Dr. George Djaiani to request detailed information for the study. The reply was that this study is finished and they are planning to analyse the data soon.

Fischer 2009

Trial name or title	Role of absolute cerebral oximetry to prevent neurocognitive injury in elderly patients undergoing cardiac surgery
Methods	Randomized, parallel-group, controlled trial (double-blind)
Participants	Inclusion criteria: adults > 65 years; elective cardiac or thoracic aortic surgery; capable and willing to consent; literate in English Exclusion criteria: emergency surgery; major neurological disease; gross cognitive dysfunction; patients not expected to be able to complete the 1 week and 3 months postoperative visit Estimated enrolment: 120
Interventions	Intervention group: once the cerebral desaturation ($SctO_2$ < 60% for 5 minutes) is established, "the study personnel will attempt to optimize the level of oxygen within the brain of the study patients." Control group: no intervention even if the $SctO_2$ falls below 60%

Fischer 2009 *(Continued)*

Outcomes	Primary outcomes: postoperative delirium and postoperative cognitive dysfunction during the first 5 days after surgery Secondary outcomes: postoperative morbidity and mortality at 3 months postoperatively
Starting date	September 2009
Contact information	Gregory Fischer, MD, Mount Sinai School of Medicine, New York, United States, 10029 Tel: 212-241-7749 Email address: gregory.fischer@mountsinai.org Dionne Bobb, M.S, CCRC Email address: dionne.bobb@mountsinai.org
Notes	ClinicalTrials.gov identifier: NCT00991328 Recruiting status: recruiting http://clinicaltrials.gov/ct2/show/study/NCT00991328 We contacted Dr. Gregory Fischer by email to request detailed information for the study, but we did not receive a reply.

Fominskiy 2014

Trial name or title	Role of cerebral oximetry in reducing postoperative morbidity following cardiac surgery
Methods	Randomized, parallel-group, controlled trial (single-blind)
Participants	Estimated enrolment:120 Inclusion criteria: high-risk cardiac surgery patients as determined by at least one of the following: age greater than or equal to 75 years on the day of screening; left ventricle ejection fraction less than 35%; use of a preoperative intraaortic balloon pump; combined valve and coronary artery surgery or multiple valve surgery in patients who have congestive heart failure, or renal insufficiency (creatinine clearance < 60 ml/min) Exclusion criteria: refusal of consent
Interventions	Intervention group: Cerebral NIRS monitoring by means of FORE-SIGHT Universal Cerebral Oximeter MC-2030C Predefined protocol of interventions for correcting rSO_2 desaturation (< 60%) during cardiac surgery and the first 6 hours after it In case of rSO_2 decrease less than 60% correct: head position; position of aortic,venous cannulae and central venous catheters; partial pressure of carbon dioxide in arterial blood < 35 mmHg; mean arterial pressure < 60 mmHg; central venous pressure > 10 mmHg; cardiac index < 2.0 l/min/m2; mixed venous oxygen saturation < 60%; haemoglobin < 65 g/L during cardiopulmonary bypass or haemoglobin < 90 g/L after cardiopulmonary bypass; decrease cerebral O_2 consumption Control group: standard treatment
Outcomes	Primary outcomes: incidence of major organ morbidity and mortality including stroke, acute kidney injury requiring dialysis, mechanical ventilation more than 48 hours, mediastinitis, reoperation

Fominskiy 2014 *(Continued)*

	and death (up to 30 day after randomization); duration of intensive care unit stay; duration of post-operative hospital stay; death from all causes at 30 days Secondary outcomes: incidence of intraoperative desaturation episodes (desaturation is defined as level of rSO_2 less than 60%); severity of intraoperative desaturation episodes (severity is defined as the product of length of time and depth of rSO_2 less than 60%)
Starting date	June 2014
Contact information	Evgeny V Fominskiy, MD, PhD, Meshalkin Research Institute of Pathology of Circulation Tel: +79139538754 Email: evfominskiy@gmail.com
Notes	ClinicalTrials.gov identifier: NCT02155868 Recruiting status: recruiting https://clinicaltrials.gov/ct2/show/NCT02155868 We contacted Dr. Evgeny V Fominskiy by email to request detailed information for the study. The reply was that they have just finished enrolling patients and are making the follow-up. The final results will be ready approximately in March 2017.

Grocott 2013

Trial name or title	Reversing cerebral oxygen desaturations greater that 10% of baseline values using NIRS in the ICU (NIRS ICU)
Methods	Randomized controlled trial (single-blind)
Participants	Inclusion criteria: adults > 18 years; patients undergoing cardiac surgery employing CPB Exclusion criteria: patients having DHCA or aorta procedures Estimated enrolment: 50
Interventions	Intervention group: "NIRS derived cerebral oximetry device (EQUANOX) used and the caregiver in the ICU will see the data in order to guide the use of the interventional algorithm to treat the cerebral desaturation" Control group: "NIRS derived cerebral oximetry device (EQUANOX) used but data not visible to ICU caregivers"
Outcomes	Primary outcomes: incidence of postoperative cerebral desaturation at 24 hours or unit discharge; endothelial function, delirium and any adverse events by phone interview on postoperation day 30
Starting date	May 2013
Contact information	Hilary P Grocott, MD, Department of Anesthesia and Surgery, University of Manitoba, St. Boniface Hospital Winnipeg, Manitoba, Canada, R2H 2A6 Tel: 204-258-1085 Email address: hgrocott@sbgh.mb.ca John R McVagh, MA

Grocott 2013 *(Continued)*

	Tel: 204-258-1380 Email address: jmcvagh@sbgh.mb.ca
Notes	ClinicalTrials.gov identifier: NCT01875055 Recruiting status: recruiting http://clinicaltrials.gov/show/NCT01875055 We have sent an email to Dr. Hilary P Grocott to check if this ongoing study was included in the Deschamps 2016 multicentre trial. The reply was that this study was not included in Deschamps 2016. We contacted Dr. Hilary P Grocott by email to request detailed information for the study. The reply was that the study has not yet been submitted for publication.

Shi 2013

Trial name or title	Cerebral oxygen directed perioperative anaesthesia management and postoperative delirium in elder patients having oesophageal cancer surgery
Methods	Randomized, parallel-group, controlled trial
Participants	Inclusion criteria: adults > 70 years; given informed consent; fluent in Chinese without serious hearing or vision impairments; scheduled for oesophagectomy; Geriatric Depression Scale score < 5; no history of neuropsychiatric disorders, alcoholism, substance abuse or intake of psychotropic medications Exclusion criteria: registered in other clinical trials; neurological and psychotic disorders; taking cholinesterase inhibitors, haloperidol or other atypical antipsychotics; diagnosed with stroke, myocardial ischaemia or heart failure in recent 6 months; contraindicated to haloperidol; head skin injury, infections or ulcers which preclude the attachment of electrodes; prolonged corrected QT (QTc) interval of 460 ms or higher for men and 470 ms or higher for women Estimated enrolment: 300 participants (150 in each arm)
Interventions	Intervention group: $rScO_2$ and BIS-guided intraoperative anaesthesia Control group: BIS-guided intraoperative anaesthesia
Outcomes	Incidence of postoperative delirium; time to the onset of postoperative delirium; duration of postoperative delirium; severity of postoperative delirium; MMSE score changes; incidence of ICU mechanical ventilation; duration of ICU mechanical ventilation; length of ICU stay; length of hospital stay; incidence of other postoperative complications; Postoperative Quality Recovery Scale; Postoperative Morbidity Survey Scale; mortality rate
Starting date	November 2013
Contact information	Sun Haijing, Dept. of Anesthesiology, Changzheng Hospital, No. 415 Fengyang Road, Shanghai 20003 China Tel: +86 13816364200 Email address: haijing4200@hotmail.com Shi Xueyin, Dept. of Anesthesiology, Changzheng Hospital, No. 415 Fengyang Road, Shanghai 20003 China Tel: +86 13601682827

Shi 2013 *(Continued)*

	Email address: shixueyin1128@163.com
Notes	Chinese Clinical Trial Registry identifier: hiCTR-TRC-13003800 Recruiting status: pending http://www.chictr.org/cn/proj/show.aspx?proj=5585 We contacted Dr. Shi Xueyin by email to request detailed information for the study. The reply was that the study has not yet finished.

Teurnier 2011

Trial name or title	Medico-economic evaluation of preoperative cerebral oximetry monitoring during carotid endarterectomy (EMOCAR)
Methods	Randomized, parallel-group, controlled trial (double-blind)
Participants	Inclusion criteria: adults > 18 years; internal carotid stenosis requiring surgery; Mini Mental State Examination > 24 during preoperative examination; informed written consent. Exclusion criteria: severe renal failure or requiring dialysis; liver failure or cirrhosis (Child class ≥ B) or prothrombin activity < 50%; heart failure (NYHA ≥ III), left ventricular ejection fraction < 40%, acute coronary syndrome; associated surgery; pregnancy; contraindication to MRI; history of allergy to modified gelatine or starch; history of allergy to adhesive part of electrode Estimated enrolment: 978
Interventions	Intervention group: Quote: "Continuous perioperative cerebral oximetry monitoring (using INVOS™ cerebral oximeter) associated with haemodynamic optimisation algorithm (excluding norepinephrine) if cerebral oximetry decrease more than 15% under the preoperative baseline." Control group: Quote: "Continuously monitored with cerebral oximeter but this latter is blinded to the medical team, the alarm switch off, and patients are managed with the standard care of the centre"
Outcomes	Primary outcomes: incidence of new cerebral ischaemic lesions up to 1 month postoperatively Secondary outcomes: incremental cost-effectiveness ratio at 4 months postoperatively; hospitalization length of stay and direct medical costs at 4 months postoperatively; neurological and neurocognitive postoperative disorders at 1 month postoperatively; postoperative quality of life (SF36, EQ5D tests) at 4 months postoperatively; cerebral desaturation threshold assessment at 4 months postoperatively
Starting date	April 2011
Contact information	Yann Le Teurnier, MD, Nantes University Hospital, Nantes, France, 44000 Tel: +33240165304 Email address: yann.leteurnier@chu-nantes.fr Bertrand Rozec, MD, Nantes University Hospital, Nantes, France, 44000 Tel: +33240165308 Email address: bertrand.rozec@chu-nantes.fr
Notes	ClinicalTrials.gov identifier: NCT01415648

Teurnier 2011 *(Continued)*

	Recruiting status: this study has been terminated (recruitment time expired) http://clinicaltrials.gov/show/NCT01415648 We contacted Dr. Yann Le Teurnier by email to request detailed information for the study. The reply was that the study has not yet been finished.

Trinh 2012

Trial name or title	Measuring and treating brain oxygen levels in open heart surgery
Methods	Randomized, parallel-group, controlled trial (single-blind)
Participants	Inclusion criteria: adults > 18 years; patients scheduled to undergo elective cardiac or thoracic aortic surgery requiring cardiopulmonary bypass Exclusion criteria: severe preoperative cognitive impairment (i.e. dementia or developmental intellectual disability); sensory or motor impairment that would preclude reliable operation of a computer and keyboard; lack of access to use computer-based cognitive evaluation; non-English speaking patients; renal failure requiring dialysis; respiratory failure requiring home oxygen use; Child's B or C hepatic failure Estimated enrolment: 500
Interventions	Intervention group: Quote: "Cerebral oxygenation levels for people in this group will be monitored and maintained above 60%. If levels decrease to below 60%, a protocol is followed to guide possible interventions to increase cerebral oxygenation levels above 60%" Control group: Quote: "Cerebral oxygenation levels for people in this group will be masked and thus doctors and care staff will not use the cerebral oxygenation levels to make any interventions. If the cerebral oxygenation levels drop to below 40%, the cerebral oxygenation levels will be unmasked so that doctors can follow the protocol to increase levels to above 60%"
Outcomes	Primary outcomes: postoperative neurocognitive decline before surgery; postoperative neurocognitive decline at 3 months and 6 months after surgery Secondary outcomes: neurological dysfunction during the hospitalization for postoperative recovery; multiple organ dysfunction during the hospitalization for postoperative recovery
Starting date	November 2011
Contact information	Muoi Trinh, MD, Icahn School of Medicine at Mount Sinai, New York, United States, 10029 Tel: 212-241-4203 Email address: muoi.trinh@mssm.edu Suzan Uysal, PhD, Icahn School of Medicine at Mount Sinai, New York, United States, 10029 Tel: 212-241-1836 Email address: suzan.uysal@mountsinai.org
Notes	ClinicalTrials.gov identifier: NCT01539382 Recruiting status: recruiting http://clinicaltrials.gov/show/NCT01539382

Trinh 2012 *(Continued)*	We contacted Dr. Muoi Trinh by email to request detailed information for the study, but we did not receive a reply.

BCP: beach chair position; CAB: coronary artery bypass; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; DHCA: deep hypothermic circulatory arrest; EQ5D: EuroQol 5-domain instrument; EQUANOX: one of the NIRS-based cerebral oximetries; FORE-SIGHT: one of the NIRS-based cerebral oximetries; ICU: intensive care unit; INVOS: one of the NIRS-based cerebral oximetries; MRI: magnetic resonance imaging; ms: millisecond; NIRS: near-infrared spectroscopy; NYHA: New York Heart Association; rSO_2: regional oxygen saturation; $SctO_2$: cerebral tissue oxygen saturation; SF36: Short Form 36-Item

DATA AND ANALYSES

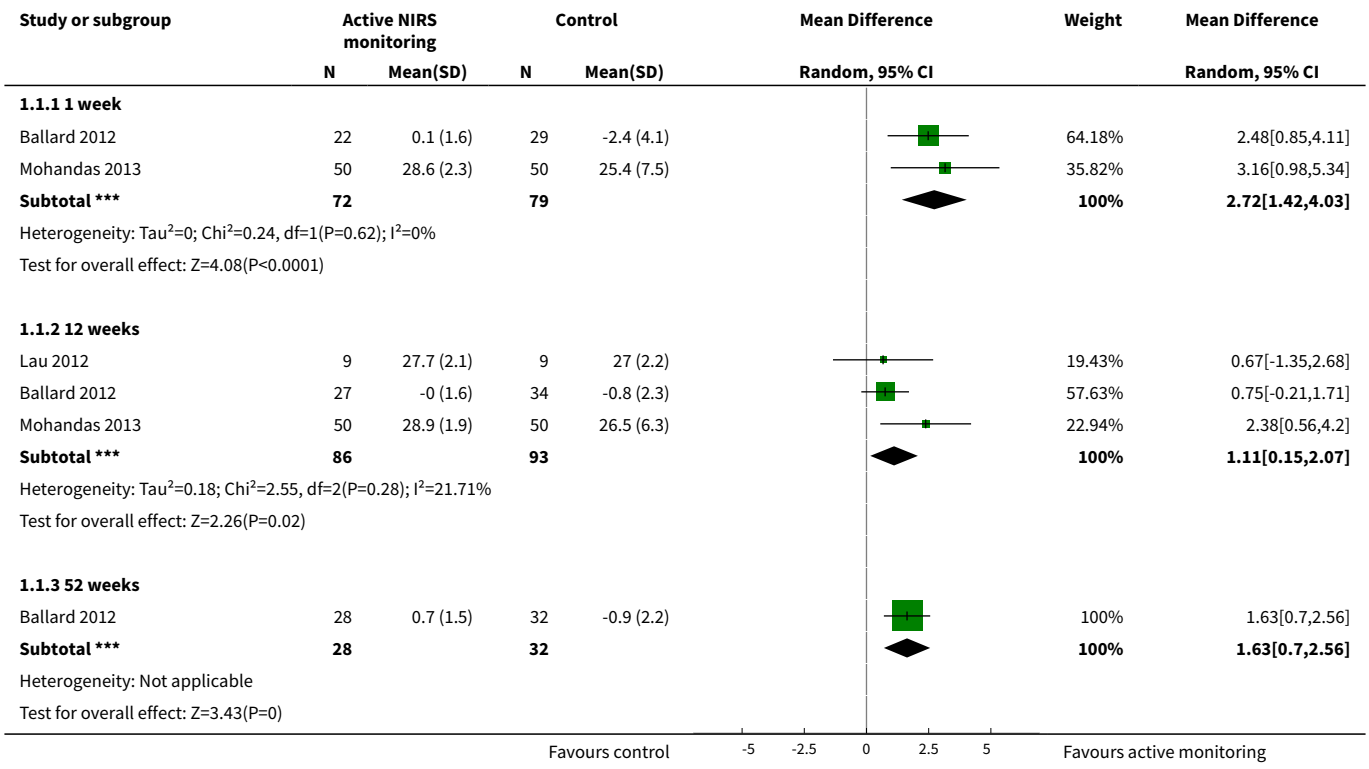
Comparison 1. Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 week	2	151	Mean Difference (IV, Random, 95% CI)	2.72 [1.42, 4.03]
1.2 12 weeks	3	179	Mean Difference (IV, Random, 95% CI)	1.11 [0.15, 2.07]
1.3 52 weeks	1	60	Mean Difference (IV, Random, 95% CI)	1.63 [0.70, 2.56]
2 POCD defined by original studies - 1 week	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mild	2	126	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.30, 0.95]
2.2 Moderate	1	47	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.20, 1.04]
2.3 Severe	2	126	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.03, 0.92]
3 POCD: decline in cognitive function - 1 week	6	962	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.37, 1.04]
4 Intraoperative mortality or postoperative mortality: Death	3	390	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.08, 5.03]
5 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 In OR	7	916	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
5.2 In ICU	2	249	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.34]

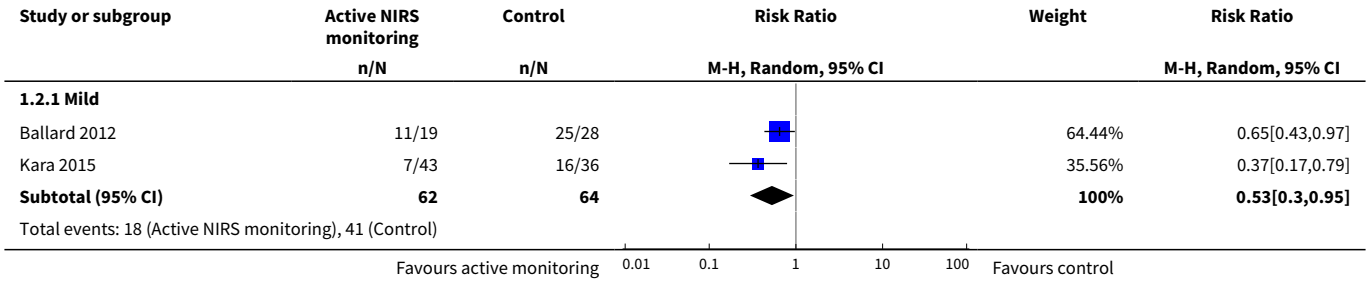
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Any major non-neurological complications as defined by individual study	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Non-specific any reported complications	6	562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
6.2 Non-specific respiratory complications	1	122	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.56]
6.3 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
6.4 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
6.5 Pneumothorax	1	150	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.05]
6.6 Postoperative acute pulmonary edema	1	40	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.01, 3.92]
6.7 Postoperative pulmonary embolism	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.8 Prolonged mechanical ventilation	1	190	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.54]
6.9 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
6.10 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
6.11 Cardiac ischaemia	1	169	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.27]
6.12 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
6.13 Reoperation for bleeding	1	200	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.77]
6.14 MOMM	1	200	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.08, 0.95]
6.15 Rupture of the colonic anastomosis	1	122	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.36, 2.83]
6.16 Surgical reintervention	1	200	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.09]
6.17 Patients experiencing more than 1 complication	1	122	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.56]
6.18 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]
6.19 Revision	1	190	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.25]
6.20 Hospital stay > 7 days (% of patients)	1	190	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.81, 1.48]
6.21 Mediastinitis	1	200	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.09]

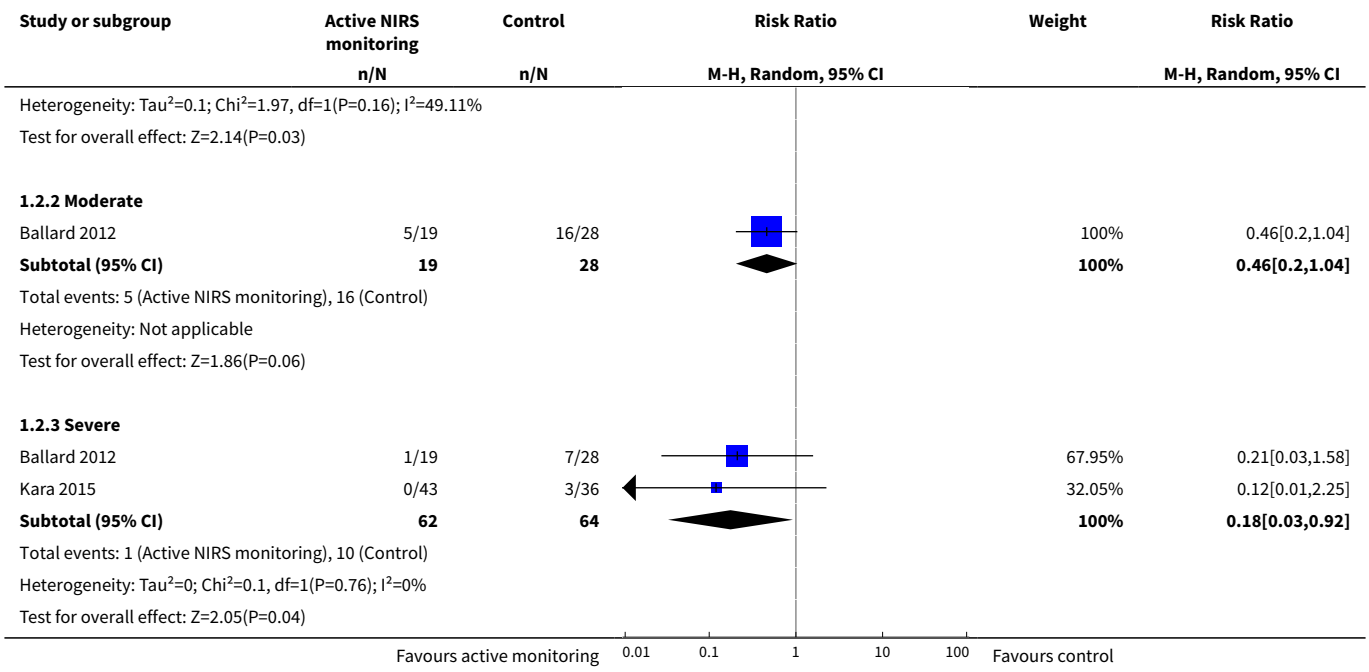
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.22 Septicaemia	1	200	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.09]
6.23 Unplanned HDU/ICU admission	1	40	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.08]
7 Length of ICU stay (days)	3	379	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.48, -0.09]

Analysis 1.1. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score).

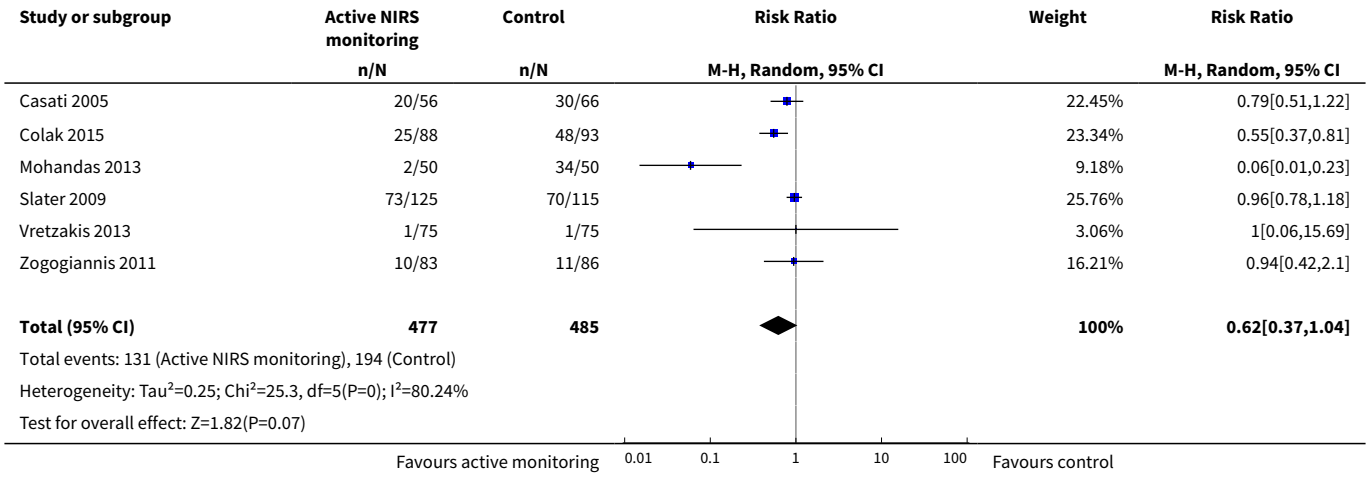


Analysis 1.2. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 2 POCD defined by original studies - 1 week.

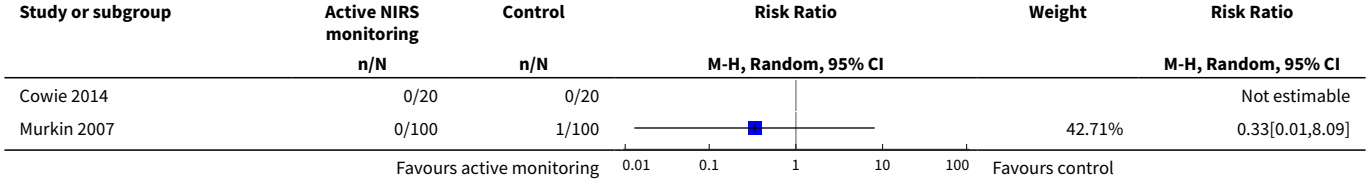


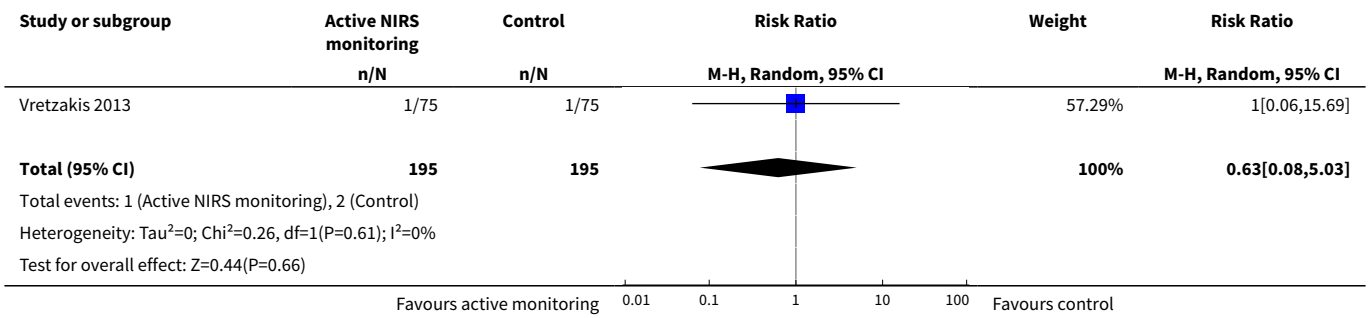


Analysis 1.3. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 3 POCD: decline in cognitive function - 1 week.

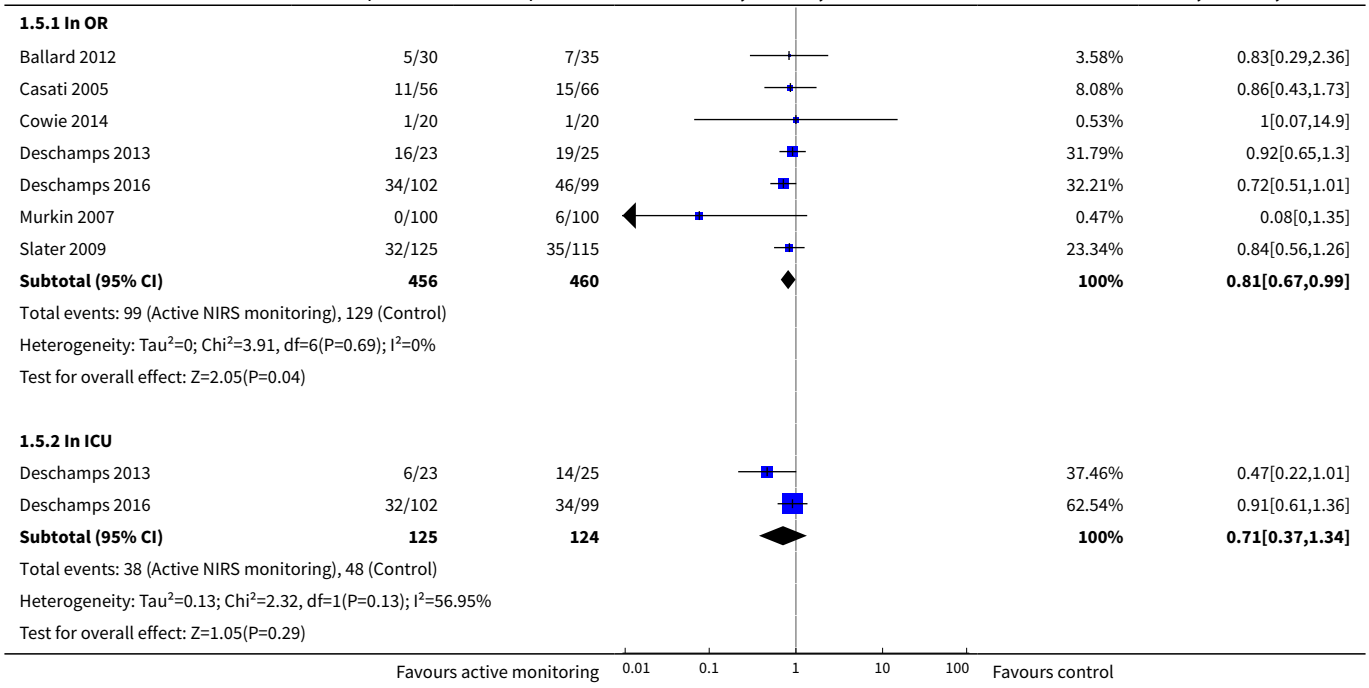


Analysis 1.4. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 4 Intraoperative mortality or postoperative mortality: Death.

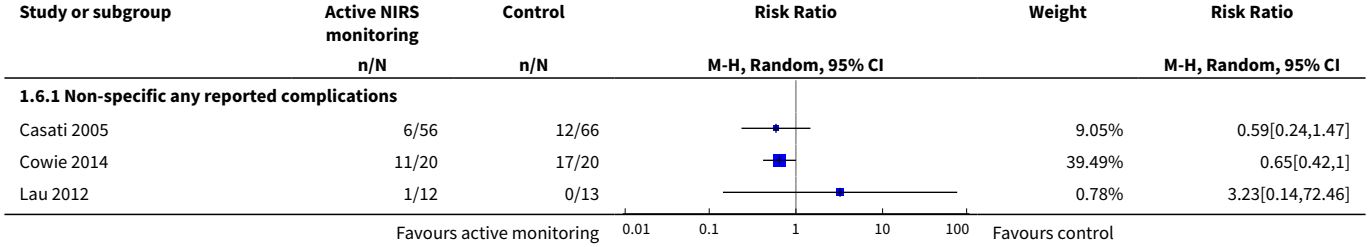


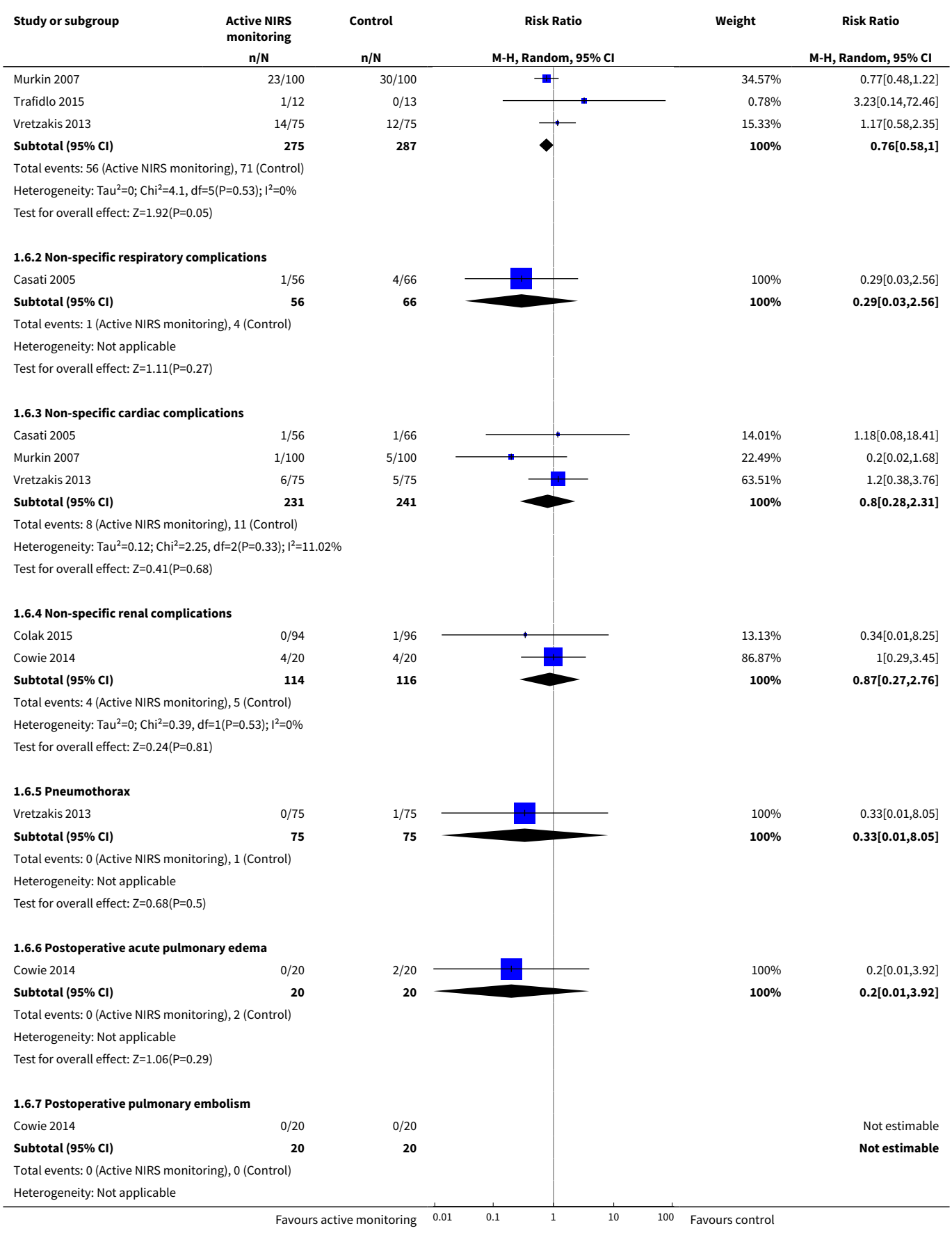


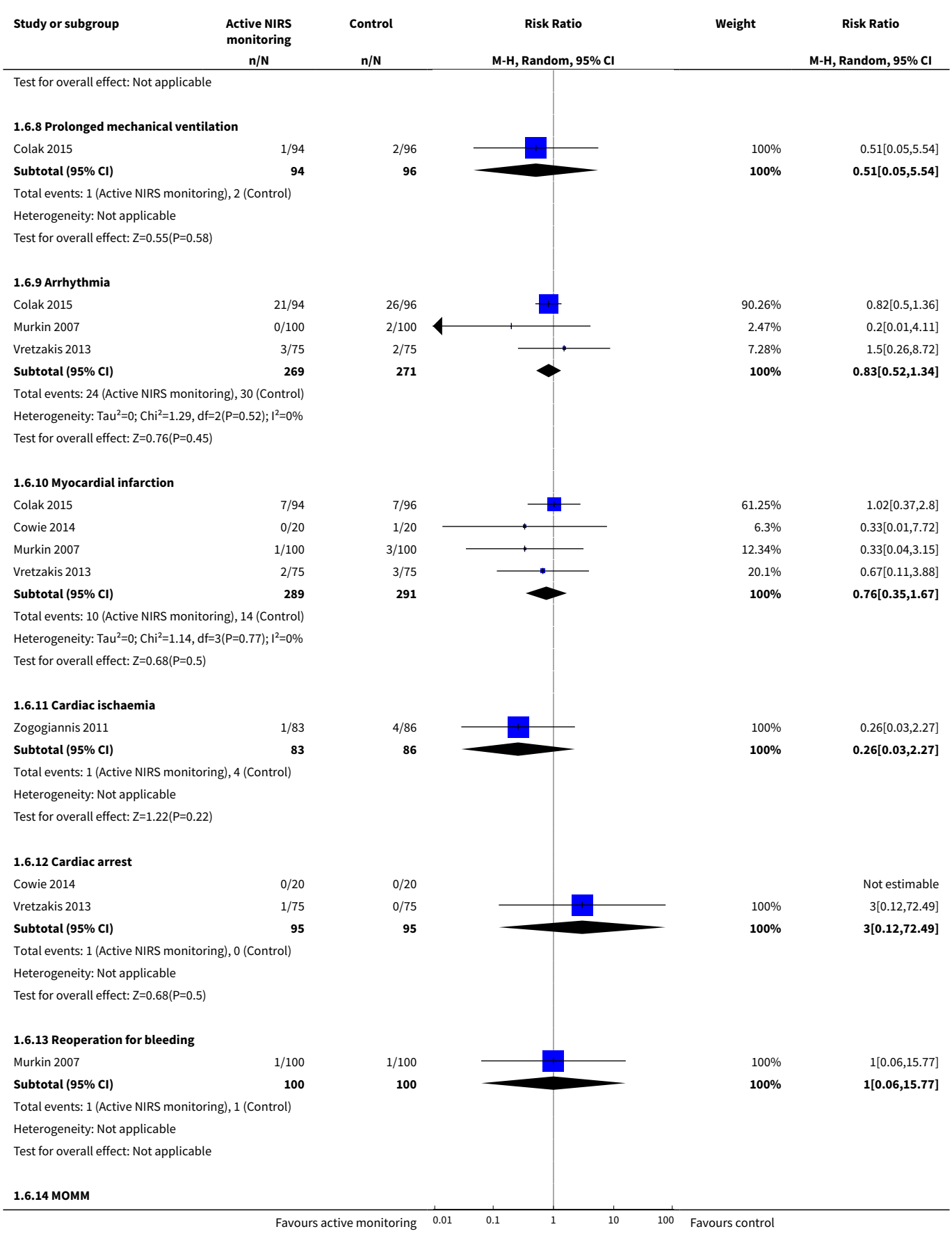
Analysis 1.5. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 5 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation.

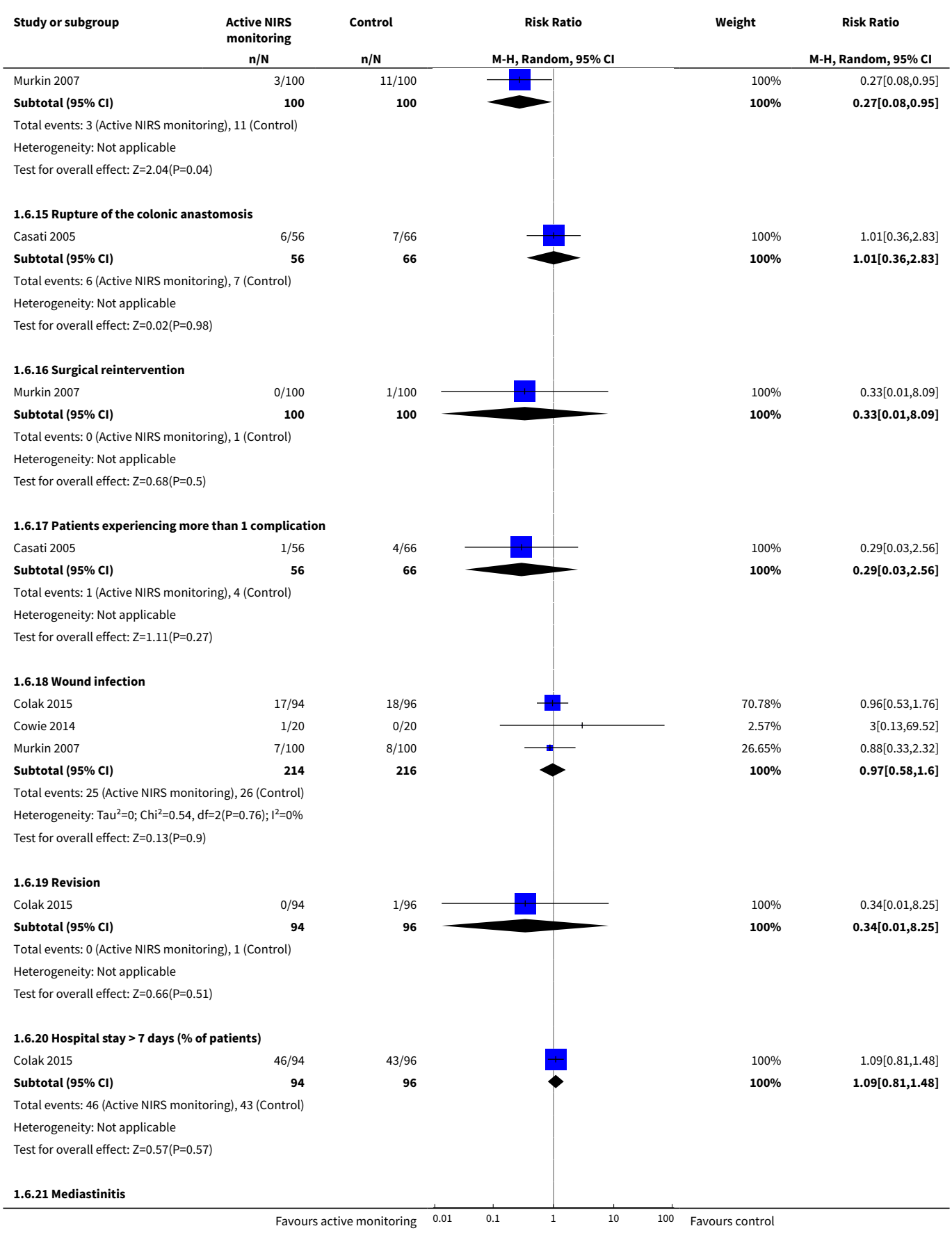


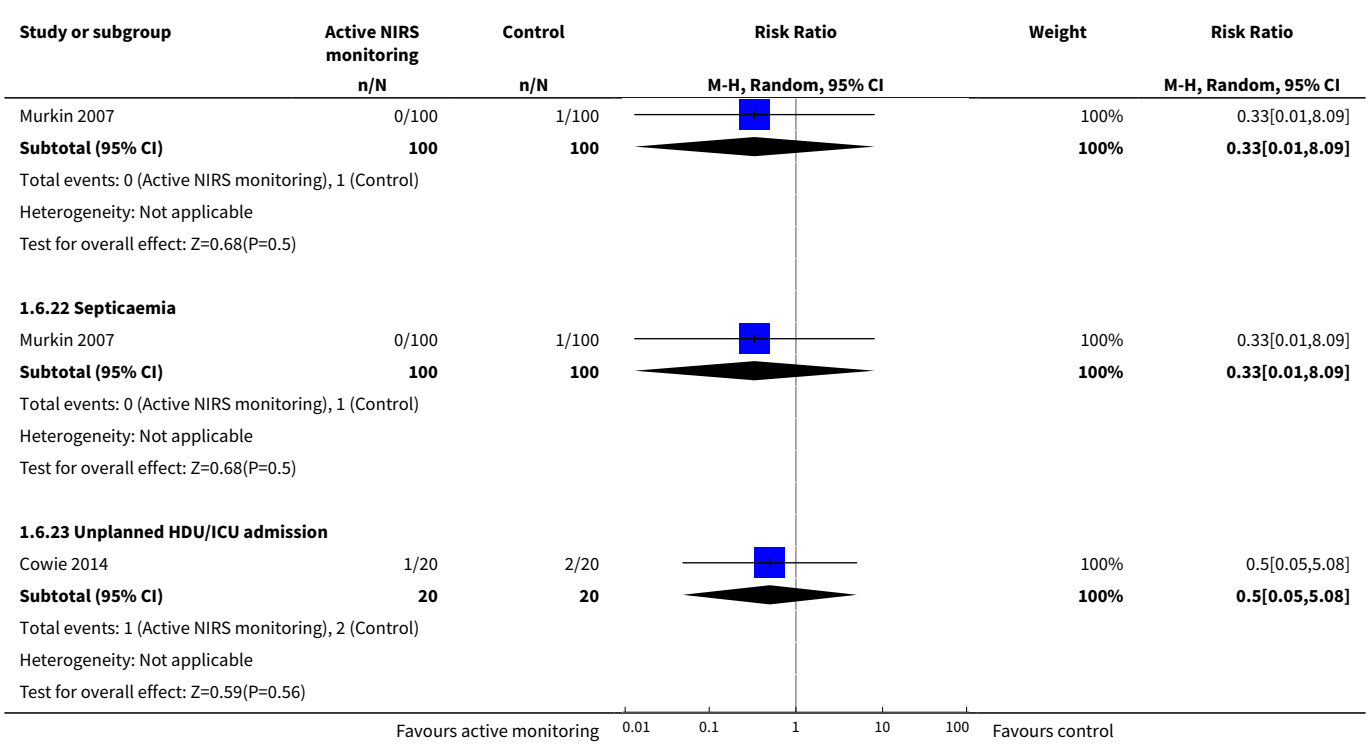
Analysis 1.6. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 6 Any major non-neurological complications as defined by individual study.



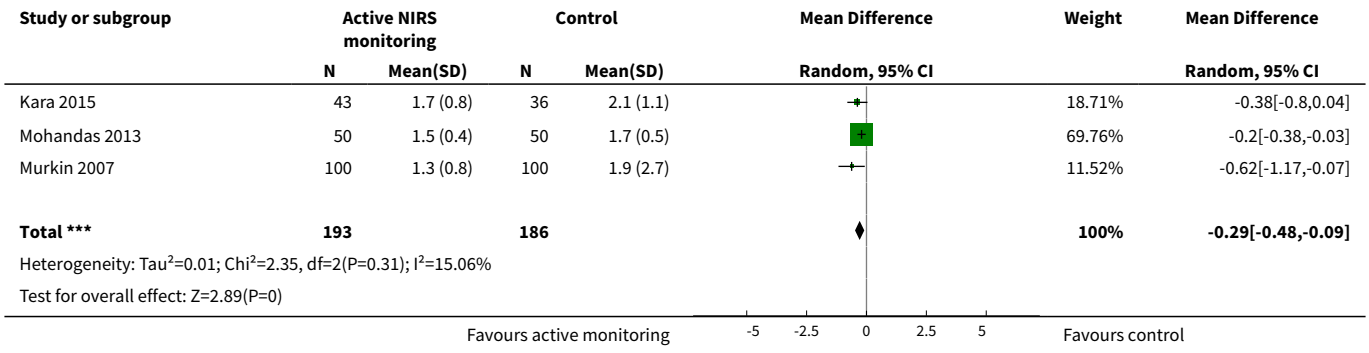








Analysis 1.7. Comparison 1 Active cerebral oxygenation monitoring vs blinded cerebral oxygenation monitoring, Outcome 7 Length of ICU stay (days).

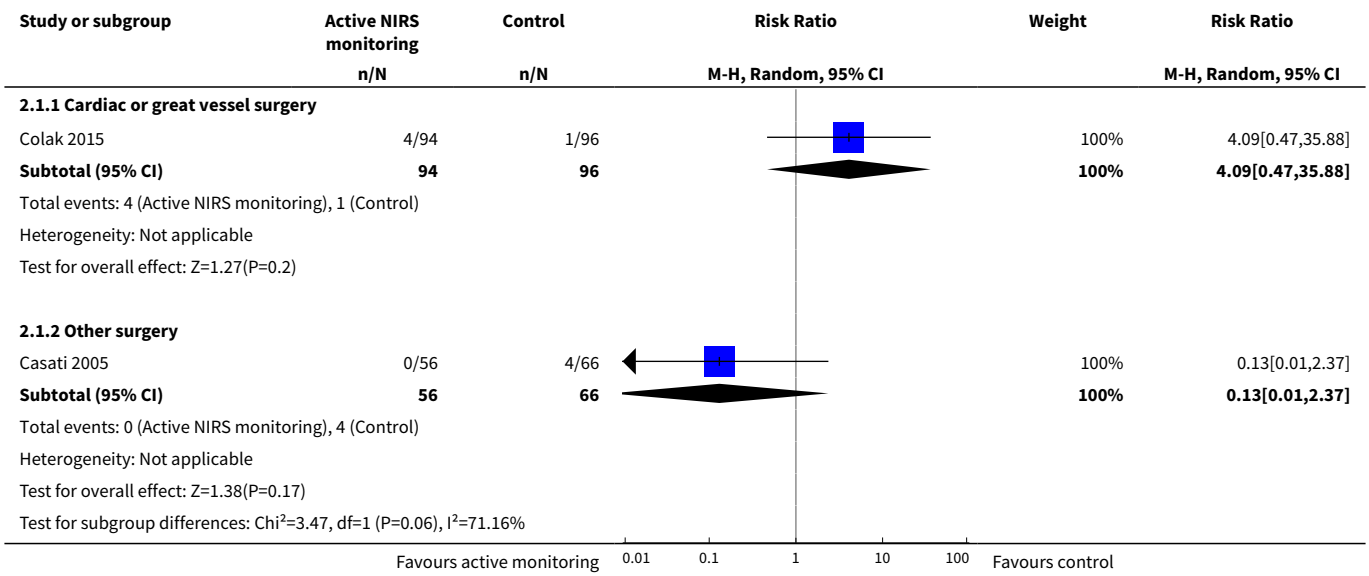


Comparison 2. Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery

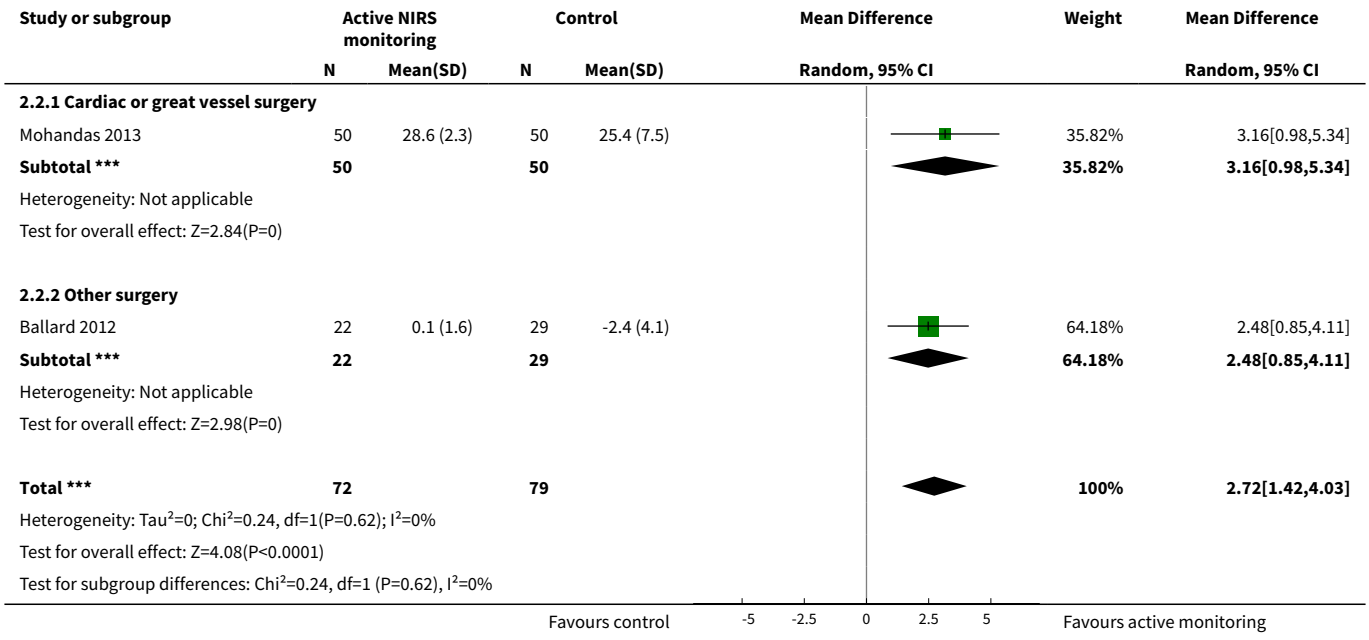
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative stroke or other neurological injury: Neurological injury	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cardiac or great vessel surgery	1	190	Risk Ratio (M-H, Random, 95% CI)	4.09 [0.47, 35.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Other surgery	1	122	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.37]
2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 1 week	2	151	Mean Difference (IV, Random, 95% CI)	2.72 [1.42, 4.03]
2.1 Cardiac or great vessel surgery	1	100	Mean Difference (IV, Random, 95% CI)	3.16 [0.98, 5.34]
2.2 Other surgery	1	51	Mean Difference (IV, Random, 95% CI)	2.48 [0.85, 4.11]
3 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks	3	179	Mean Difference (IV, Random, 95% CI)	1.11 [0.15, 2.07]
3.1 Cardiac or great vessel surgery	2	118	Mean Difference (IV, Random, 95% CI)	1.58 [-0.10, 3.25]
3.2 Other surgery	1	61	Mean Difference (IV, Random, 95% CI)	0.75 [-0.21, 1.71]
4 POCD defined by original studies - 1 week - mild	2	126	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.30, 0.95]
4.1 Cardiac or great vessel surgery	1	79	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.17, 0.79]
4.2 Other surgery	1	47	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.43, 0.97]
5 POCD defined by original studies - 1 week - severe	2	126	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.03, 0.92]
5.1 Cardiac or great vessel surgery	1	79	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.25]
5.2 Other surgery	1	47	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.03, 1.58]
6 POCD: decline in cognitive function - 1 week	6	962	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.37, 1.04]
6.1 Cardiac or great vessel surgery	4	671	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.19, 1.11]
6.2 Carotid endarterectomy	1	169	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.42, 2.10]
6.3 Other surgery	1	122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.51, 1.22]

Analysis 2.1. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 1 Postoperative stroke or other neurological injury: Neurological injury.

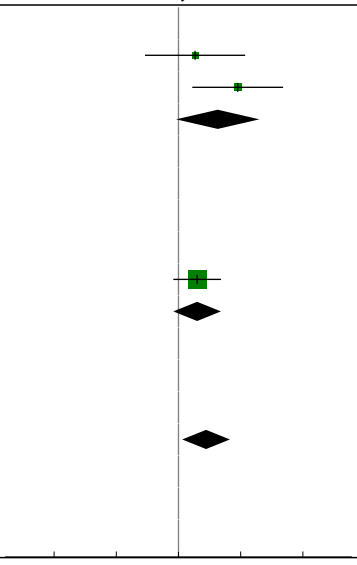


Analysis 2.2. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 1 week.



Analysis 2.3. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 3 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks.

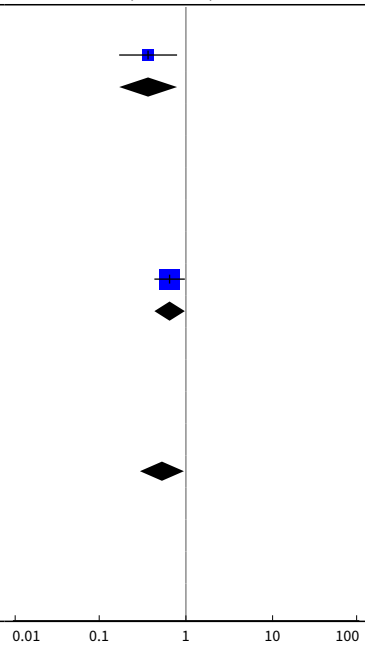
Study or subgroup	Active NIRS monitoring N	Active NIRS monitoring Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.3.1 Cardiac or great vessel surgery							
Lau 2012	9	27.7 (2.1)	9	27 (2.2)		19.43%	0.67[-1.35,2.68]
Mohandas 2013	50	28.9 (1.9)	50	26.5 (6.3)		22.94%	2.38[0.56,4.2]
Subtotal ***	**59**		**59**			**42.37%**	**1.58[-0.1,3.25]**
Heterogeneity: Tau^2=0.51; Chi^2=1.53, df=1(P=0.22); I^2=34.49%							
Test for overall effect: Z=1.85(P=0.06)							
2.3.2 Other surgery							
Ballard 2012	27	-0 (1.6)	34	-0.8 (2.3)		57.63%	0.75[-0.21,1.71]
Subtotal ***	**27**		**34**			**57.63%**	**0.75[-0.21,1.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.53(P=0.13)							
Total ***	**86**		**93**			**100%**	**1.11[0.15,2.07]**
Heterogeneity: Tau^2=0.18; Chi^2=2.55, df=2(P=0.28); I^2=21.71%							
Test for overall effect: Z=2.26(P=0.02)							
Test for subgroup differences: Chi^2=0.71, df=1 (P=0.4), I^2=0%							



Favours control — Favours active monitoring

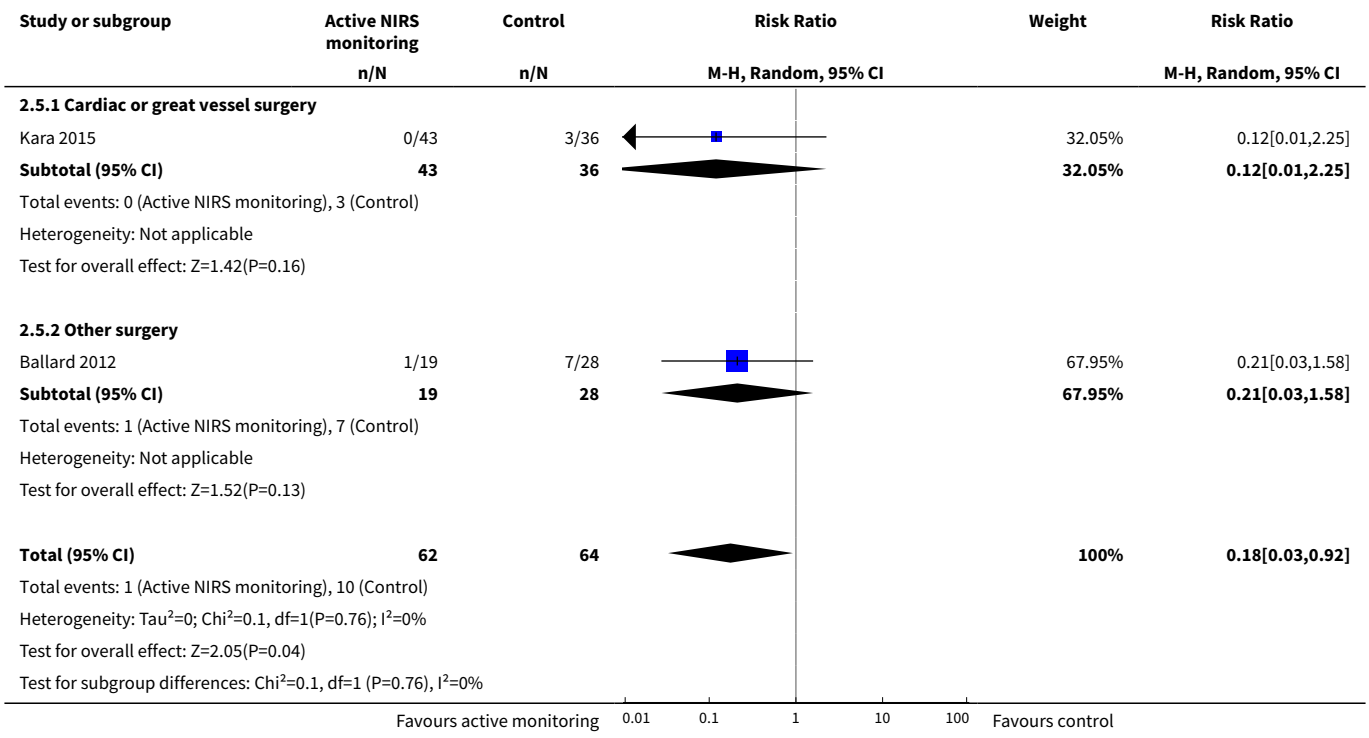
Analysis 2.4. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 4 POCD defined by original studies - 1 week - mild.

Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Cardiac or great vessel surgery					
Kara 2015	7/43	16/36		35.56%	0.37[0.17,0.79]
Subtotal (95% CI)	**43**	**36**		**35.56%**	**0.37[0.17,0.79]**
Total events: 7 (Active NIRS monitoring), 16 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.56(P=0.01)					
2.4.2 Other surgery					
Ballard 2012	11/19	25/28		64.44%	0.65[0.43,0.97]
Subtotal (95% CI)	**19**	**28**		**64.44%**	**0.65[0.43,0.97]**
Total events: 11 (Active NIRS monitoring), 25 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.1(P=0.04)					
Total (95% CI)	**62**	**64**		**100%**	**0.53[0.3,0.95]**
Total events: 18 (Active NIRS monitoring), 41 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=1.97, df=1(P=0.16); I^2=49.11%					
Test for overall effect: Z=2.14(P=0.03)					
Test for subgroup differences: Chi^2=1.66, df=1 (P=0.2), I^2=39.64%					

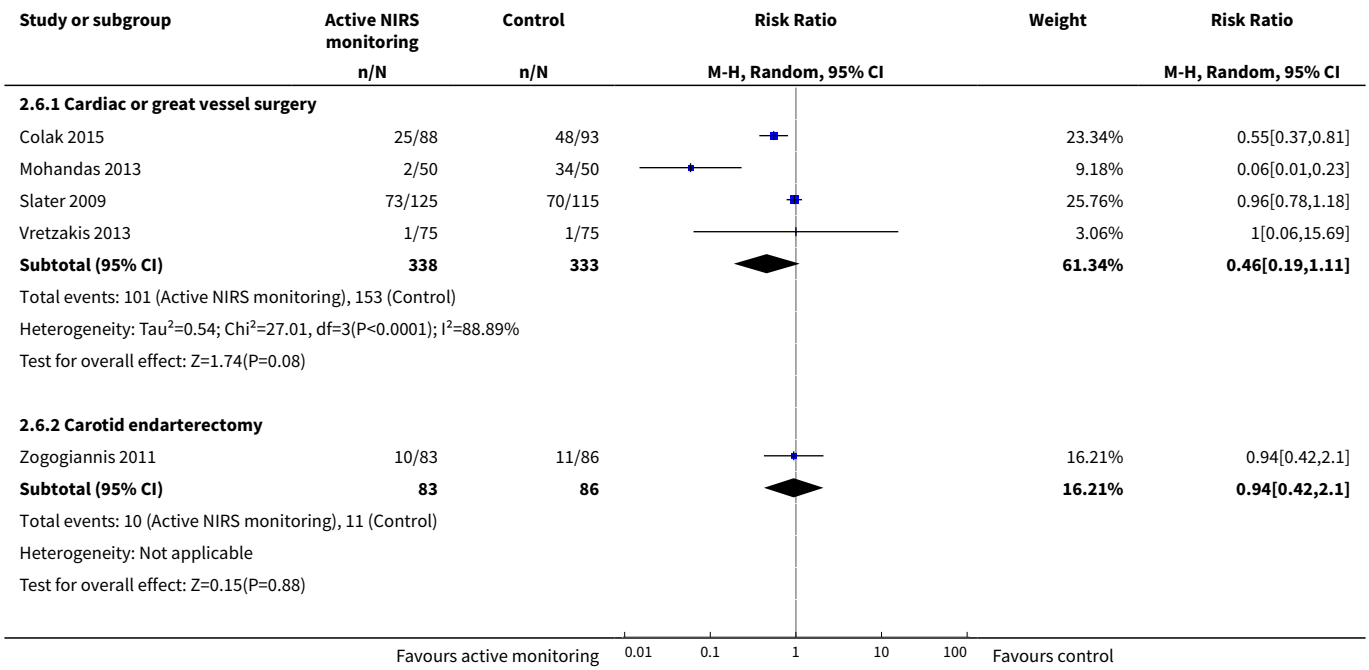


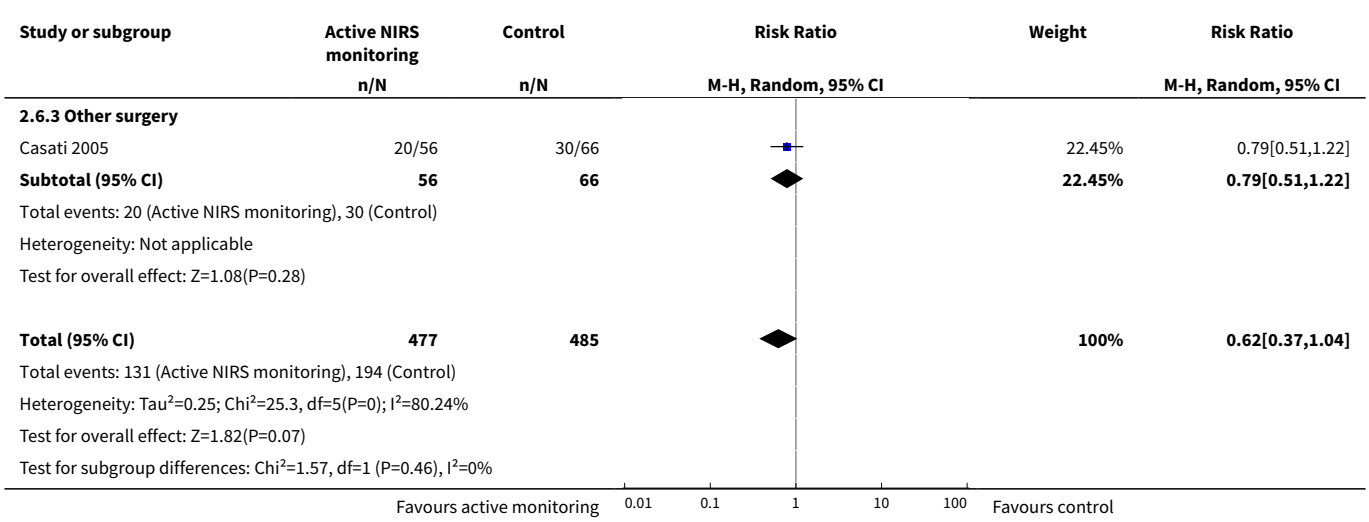
Favours active monitoring — Favours control

Analysis 2.5. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 5 POCD defined by original studies - 1 week - severe.



Analysis 2.6. Comparison 2 Subgroup of participants: participants with carotid endarterectomy, cardiac or great vessel surgery, or other surgery, Outcome 6 POCD: decline in cognitive function - 1 week.



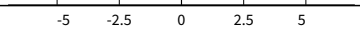


Comparison 3. Subgroup of interventions: cerebral oxygenation monitoring (EQUANOX) or INVOS vs blinded monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 1 week	2	151	Mean Difference (IV, Random, 95% CI)	2.72 [1.42, 4.03]
1.1 INVOS	1	51	Mean Difference (IV, Random, 95% CI)	2.48 [0.85, 4.11]
1.2 EQUANOX	1	100	Mean Difference (IV, Random, 95% CI)	3.16 [0.98, 5.34]
2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks	3	179	Mean Difference (IV, Random, 95% CI)	1.11 [0.15, 2.07]
2.1 INVOS	2	79	Mean Difference (IV, Random, 95% CI)	0.73 [-0.13, 1.60]
2.2 EQUANOX	1	100	Mean Difference (IV, Random, 95% CI)	2.38 [0.56, 4.20]
3 POCD: decline in cognitive function - 1 week	6	962	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.37, 1.04]
3.1 INVOS	5	862	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.04]
3.2 EQUANOX	1	100	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.23]

Analysis 3.1. Comparison 3 Subgroup of interventions: cerebral oxygenation monitoring (EQUANOX) or INVOS vs blinded monitoring, Outcome 1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 1 week.

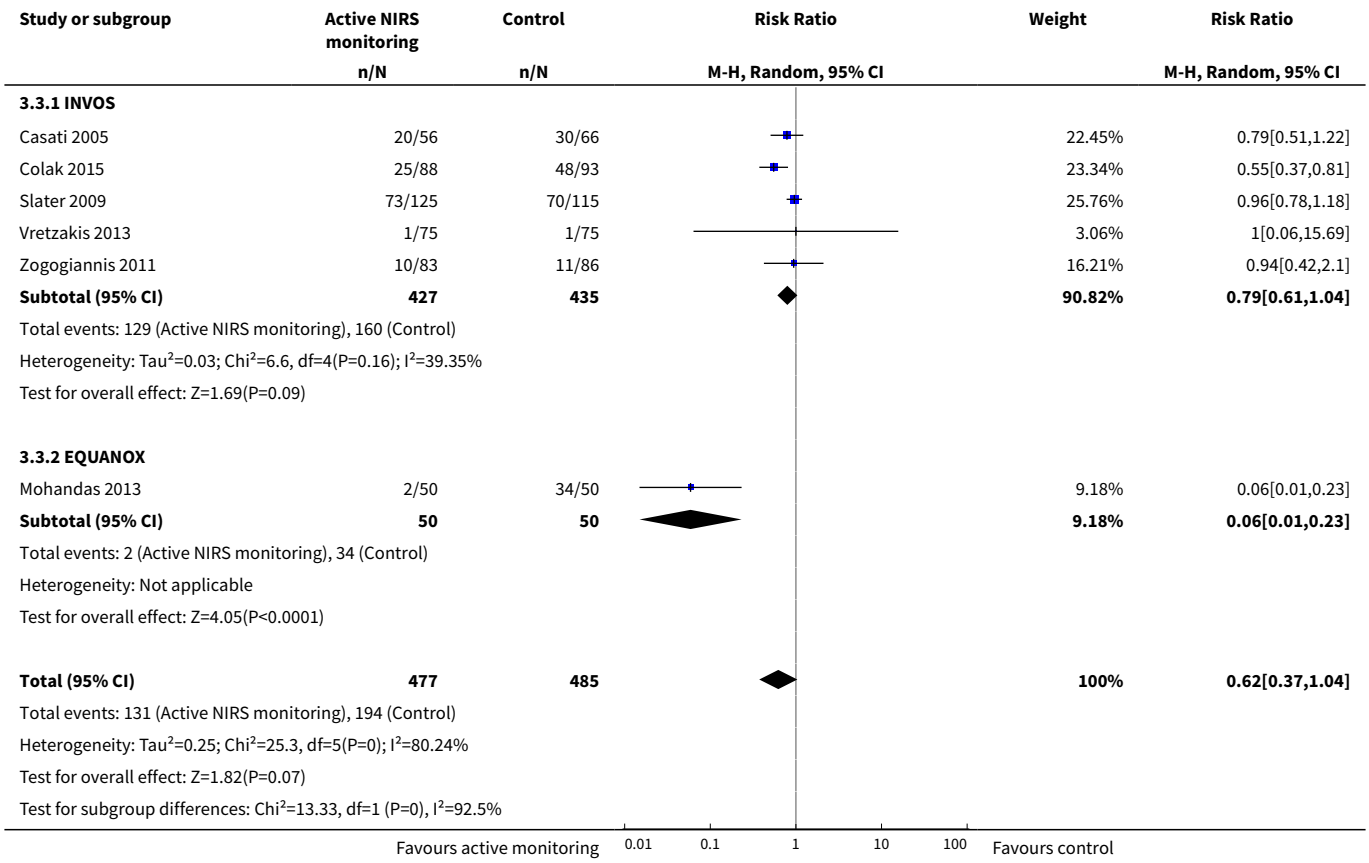
Study or subgroup	Active NIRS monitoring		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
3.1.1 INVOS							
Ballard 2012	22	0.1 (1.6)	29	-2.4 (4.1)		64.18%	2.48[0.85,4.11]
Subtotal ***	**22**		**29**			**64.18%**	**2.48[0.85,4.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.98(P=0)							
3.1.2 EQUANOX							
Mohandas 2013	50	28.6 (2.3)	50	25.4 (7.5)		35.82%	3.16[0.98,5.34]
Subtotal ***	**50**		**50**			**35.82%**	**3.16[0.98,5.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.84(P=0)							
Total ***	**72**		**79**			**100%**	**2.72[1.42,4.03]**
Heterogeneity: Tau^2=0; Chi^2=0.24, df=1(P=0.62); I^2=0%							
Test for overall effect: Z=4.08(P<0.0001)							
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.62), I^2=0%							



Analysis 3.2. Comparison 3 Subgroup of interventions: cerebral oxygenation monitoring (EQUANOX) or INVOS vs blinded monitoring, Outcome 2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score) - 12 weeks.

Study or subgroup	Active NIRS monitoring		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
3.2.1 INVOS							
Ballard 2012	27	-0 (1.6)	34	-0.8 (2.3)		57.63%	0.75[-0.21,1.71]
Lau 2012	9	27.7 (2.1)	9	27 (2.2)		19.43%	0.67[-1.35,2.68]
Subtotal ***	**36**		**43**			**77.06%**	**0.73[-0.13,1.6]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%							
Test for overall effect: Z=1.66(P=0.1)							
3.2.2 EQUANOX							
Mohandas 2013	50	28.9 (1.9)	50	26.5 (6.3)		22.94%	2.38[0.56,4.2]
Subtotal ***	**50**		**50**			**22.94%**	**2.38[0.56,4.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.56(P=0.01)							
Total ***	**86**		**93**			**100%**	**1.11[0.15,2.07]**
Heterogeneity: Tau^2=0.18; Chi^2=2.55, df=2(P=0.28); I^2=21.71%							
Test for overall effect: Z=2.26(P=0.02)							
Test for subgroup differences: Chi^2=2.55, df=1 (P=0.11), I^2=60.77%							

Analysis 3.3. Comparison 3 Subgroup of interventions: cerebral oxygenation monitoring (EQUANOX) or INVOS vs blinded monitoring, Outcome 3 POCD: decline in cognitive function - 1 week.

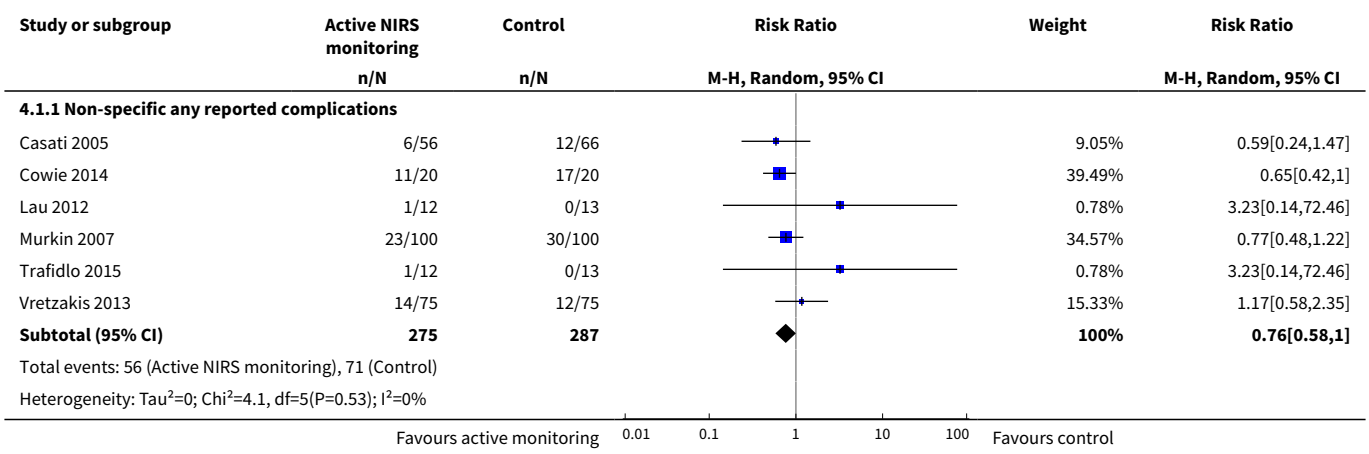


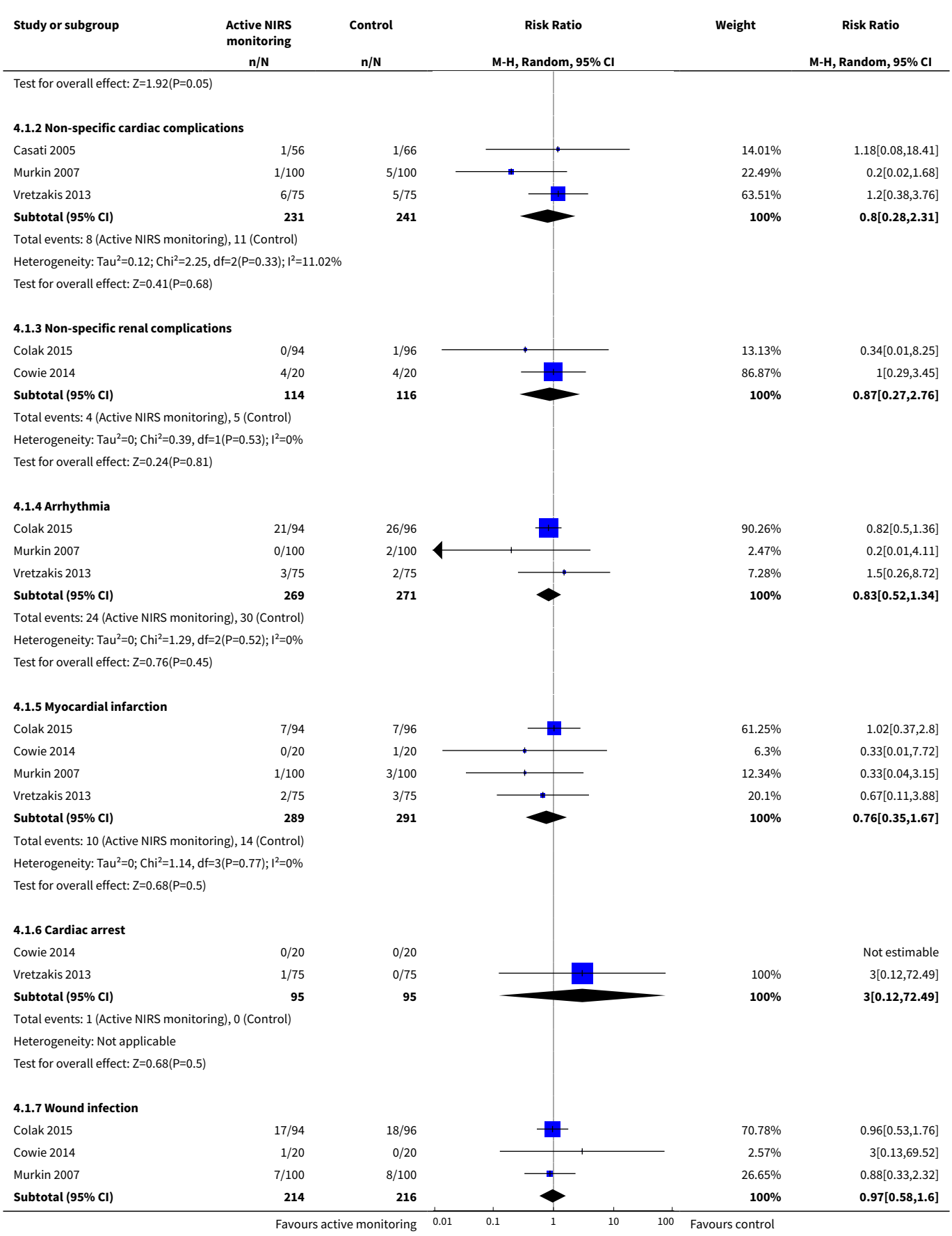
Comparison 4. Sensitivity analysis: detection bias

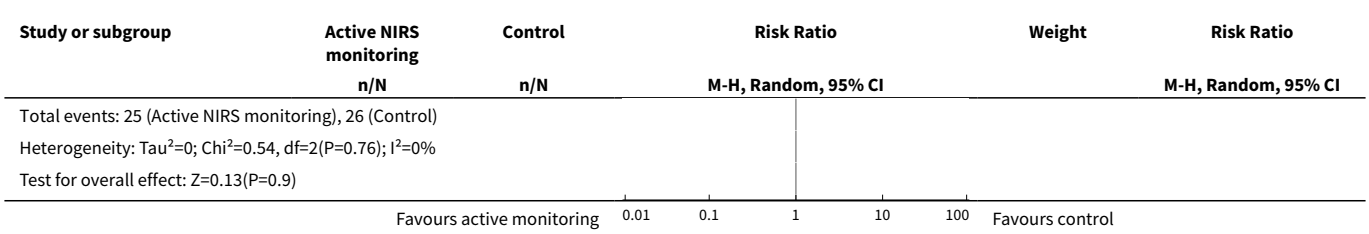
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any major non-neurological complications as defined by individual study: including studies with detection bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Non-specific any reported complications	6	562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
1.2 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
1.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
1.4 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
1.6 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
1.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]
2 Any major non-neurological complications as defined by individual study: including studies without detection bias	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Non-specific any reported complications	5	537	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 0.99]
2.2 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
2.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
2.4 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
2.5 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
2.6 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
2.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]

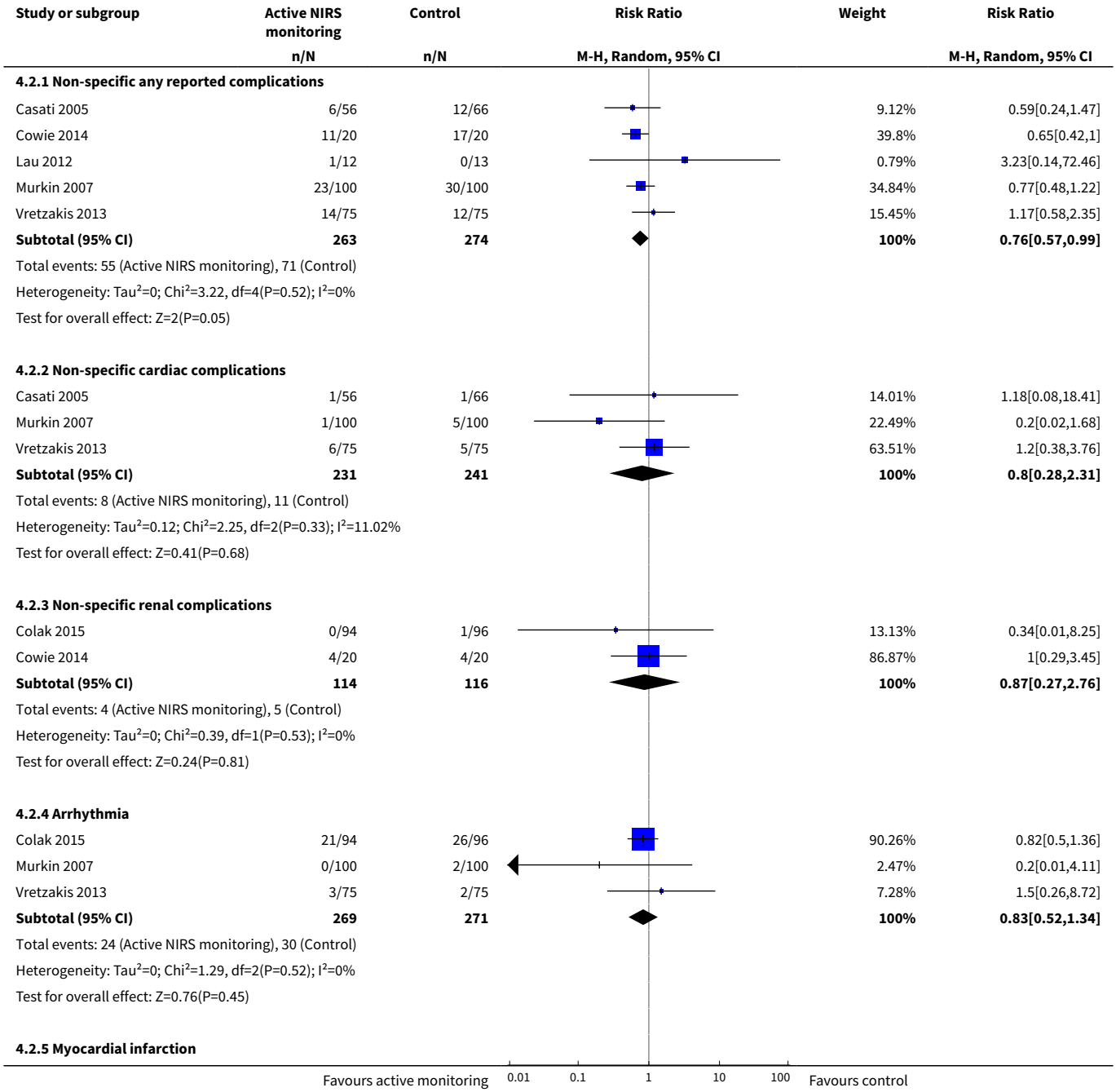
Analysis 4.1. Comparison 4 Sensitivity analysis: detection bias, Outcome 1 Any major non-neurological complications as defined by individual study: including studies with detection bias.

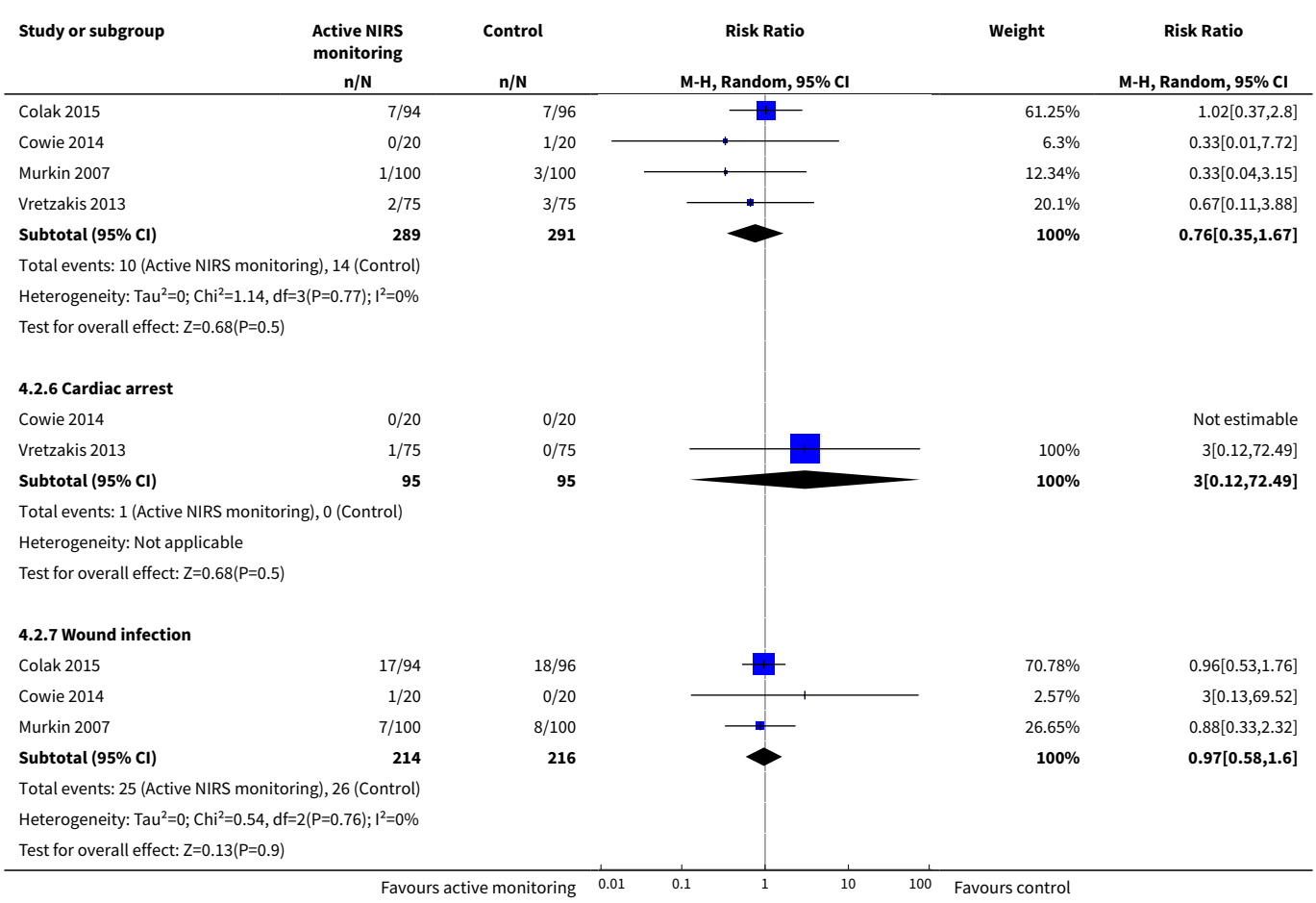






Analysis 4.2. Comparison 4 Sensitivity analysis: detection bias, Outcome 2 Any major non-neurological complications as defined by individual study: including studies without detection bias.





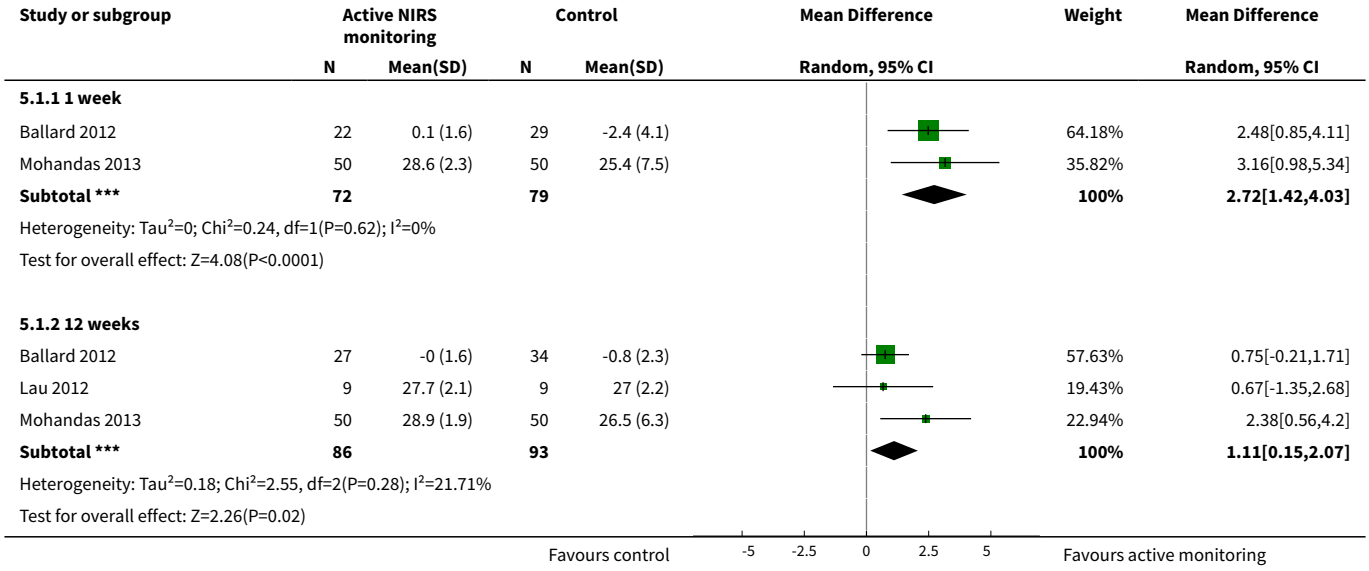
Comparison 5. Sensitivity analysis: missing data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies with missing data	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 week	2	151	Mean Difference (IV, Random, 95% CI)	2.72 [1.42, 4.03]
1.2 12 weeks	3	179	Mean Difference (IV, Random, 95% CI)	1.11 [0.15, 2.07]
2 POCD: decline in cognitive function - 1 week: including studies with missing data	6	962	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.37, 1.04]
3 Occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies with missing data	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

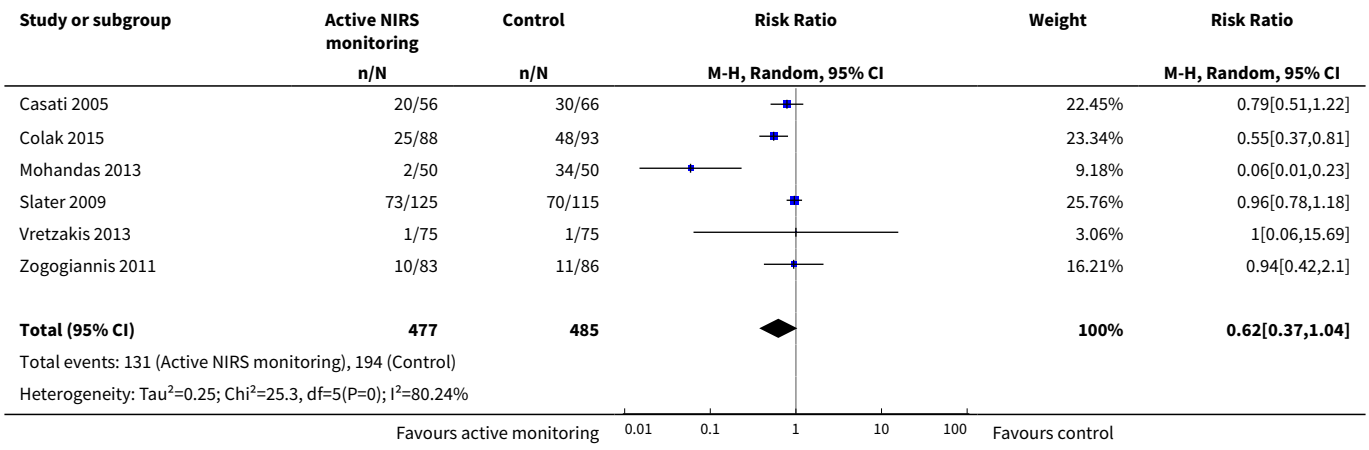
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 In OR	7	916	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
3.2 In ICU	2	249	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.34]
4 Any major non-neurological complications as defined by individual study: including studies with missing data	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Non-specific any reported complications	6	562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
4.2 Non-specific respiratory complications	1	122	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.56]
4.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
4.4 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
4.5 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
4.6 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
4.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]
5 POCD: decline in cognitive function - 1 week: without missing data	5	781	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.21]
6 Occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: without missing data	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 In OR	6	851	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
6.2 In ICU	2	249	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.34]
7 Any major non-neurological complications as defined by individual study: without missing data	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Non-specific any reported complications	5	537	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 0.99]
7.2 Non-specific respiratory complications	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.29, 3.45]

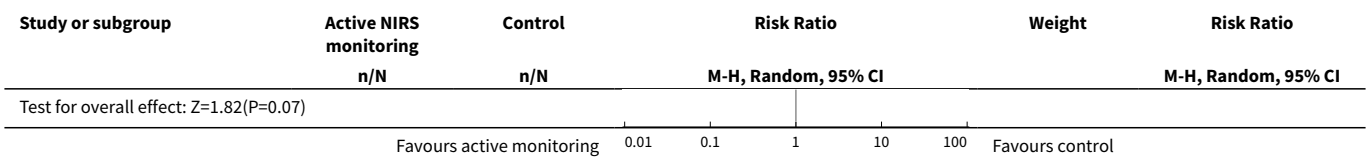
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Arrhythmia	2	350	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.13, 5.12]
7.4 Myocardial infarction	3	390	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.13, 1.70]
7.5 Wound infection	2	240	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.48]

Analysis 5.1. Comparison 5 Sensitivity analysis: missing data, Outcome 1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies with missing data.

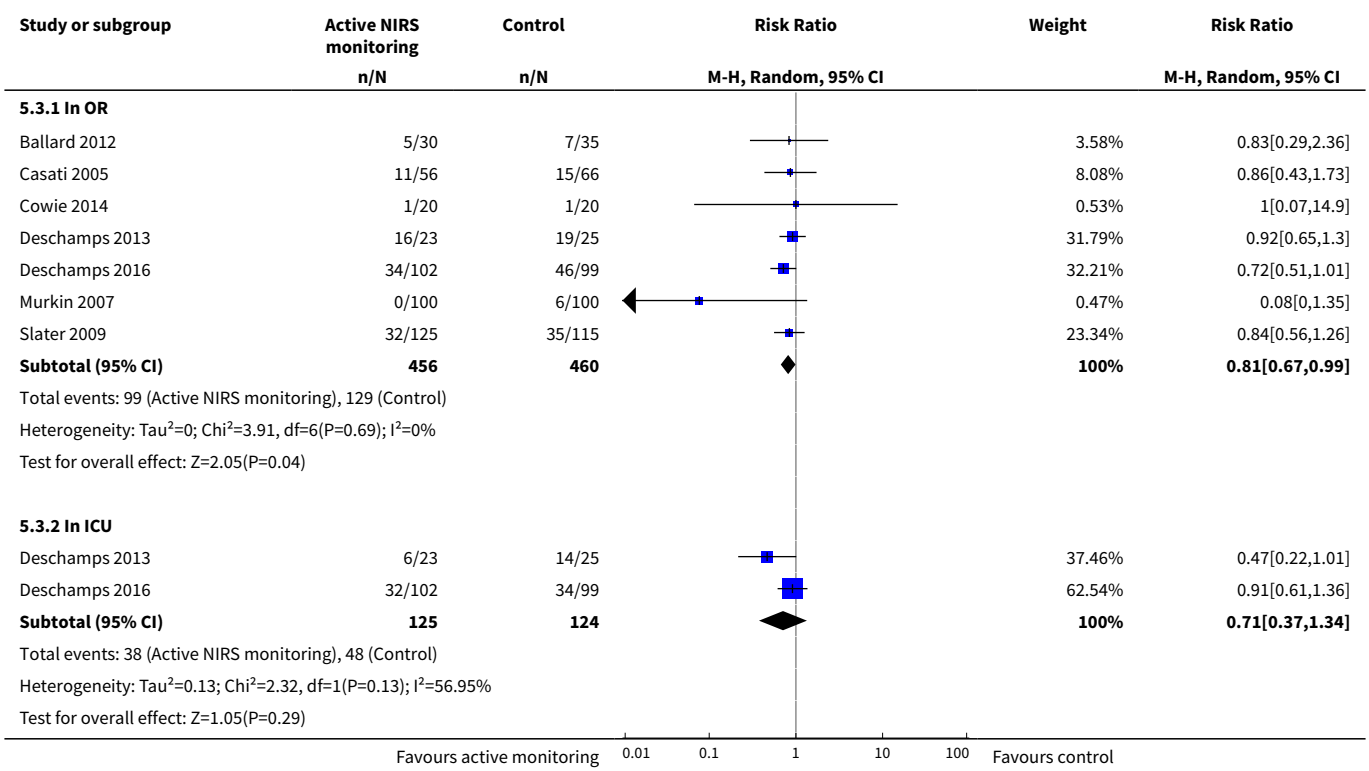


Analysis 5.2. Comparison 5 Sensitivity analysis: missing data, Outcome 2 POCD: decline in cognitive function - 1 week: including studies with missing data.

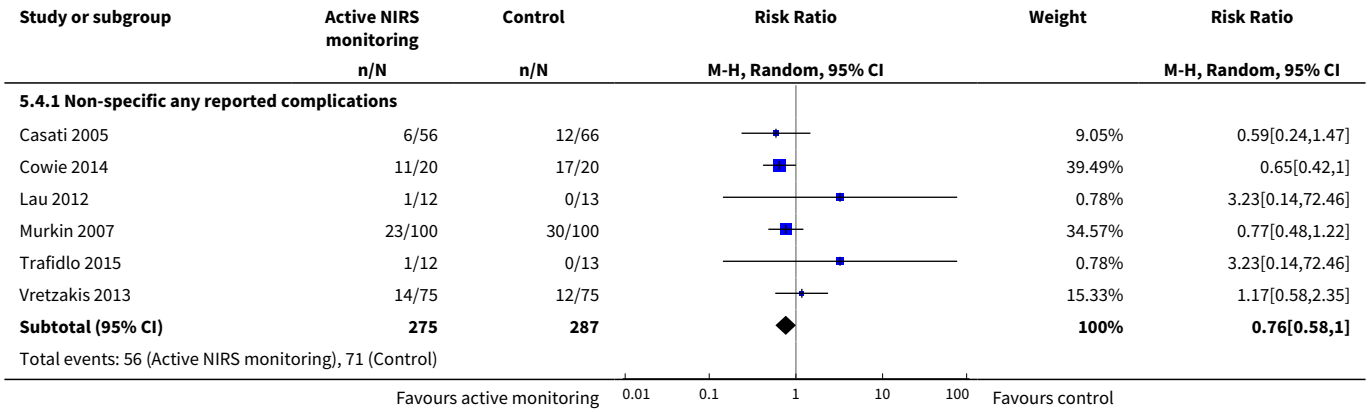


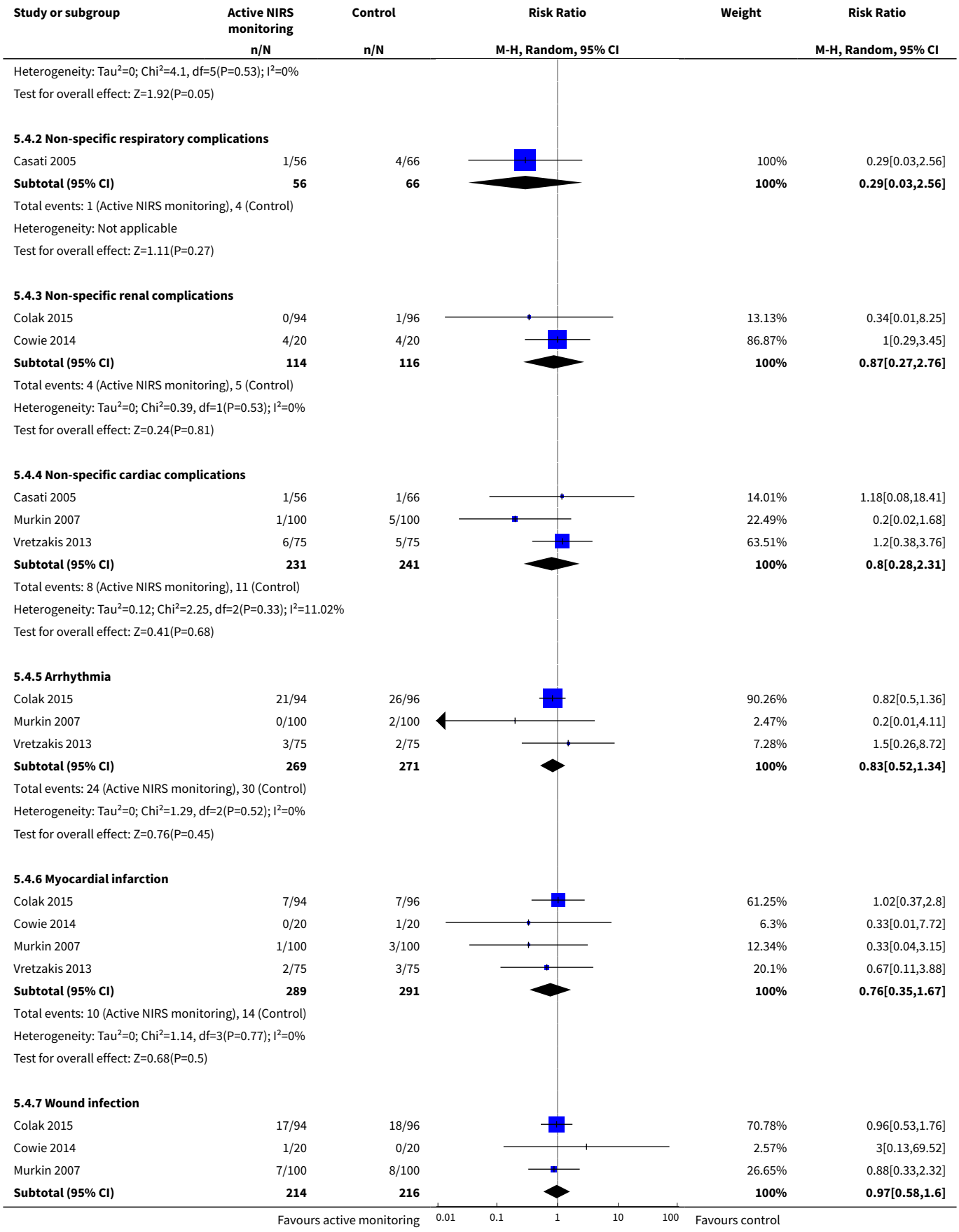


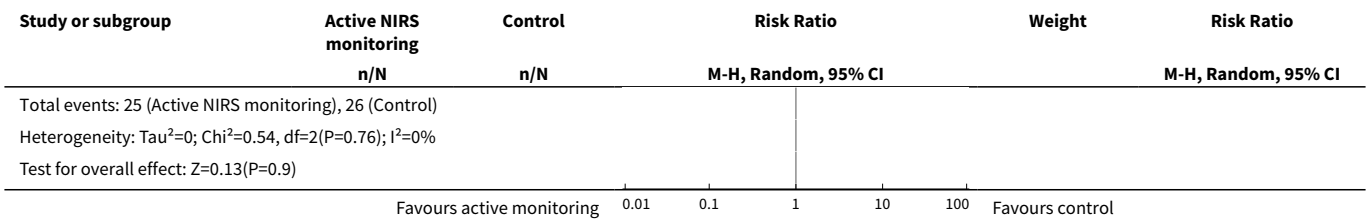
Analysis 5.3. Comparison 5 Sensitivity analysis: missing data, Outcome 3 Occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies with missing data.



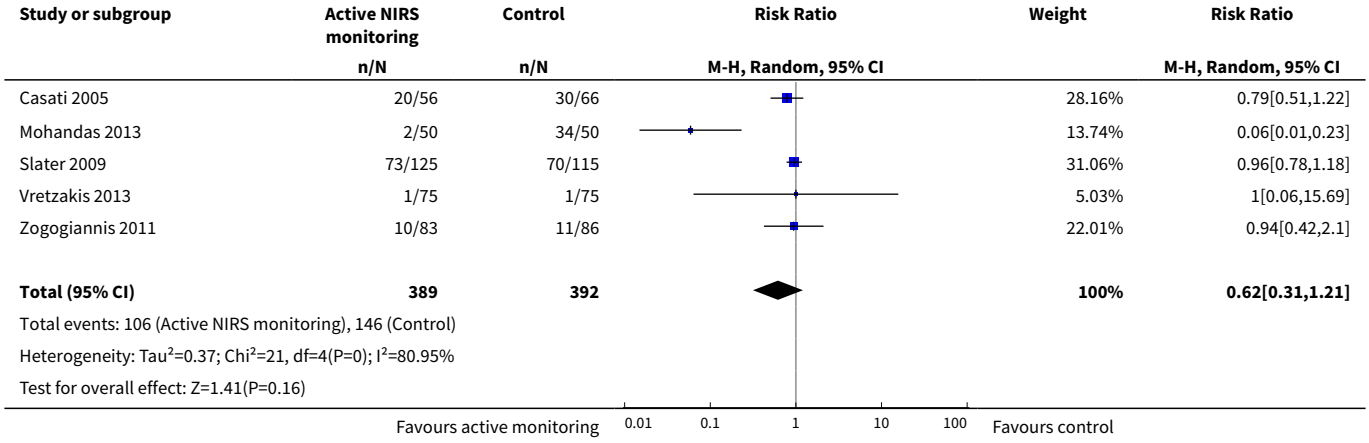
Analysis 5.4. Comparison 5 Sensitivity analysis: missing data, Outcome 4 Any major non-neurological complications as defined by individual study: including studies with missing data.



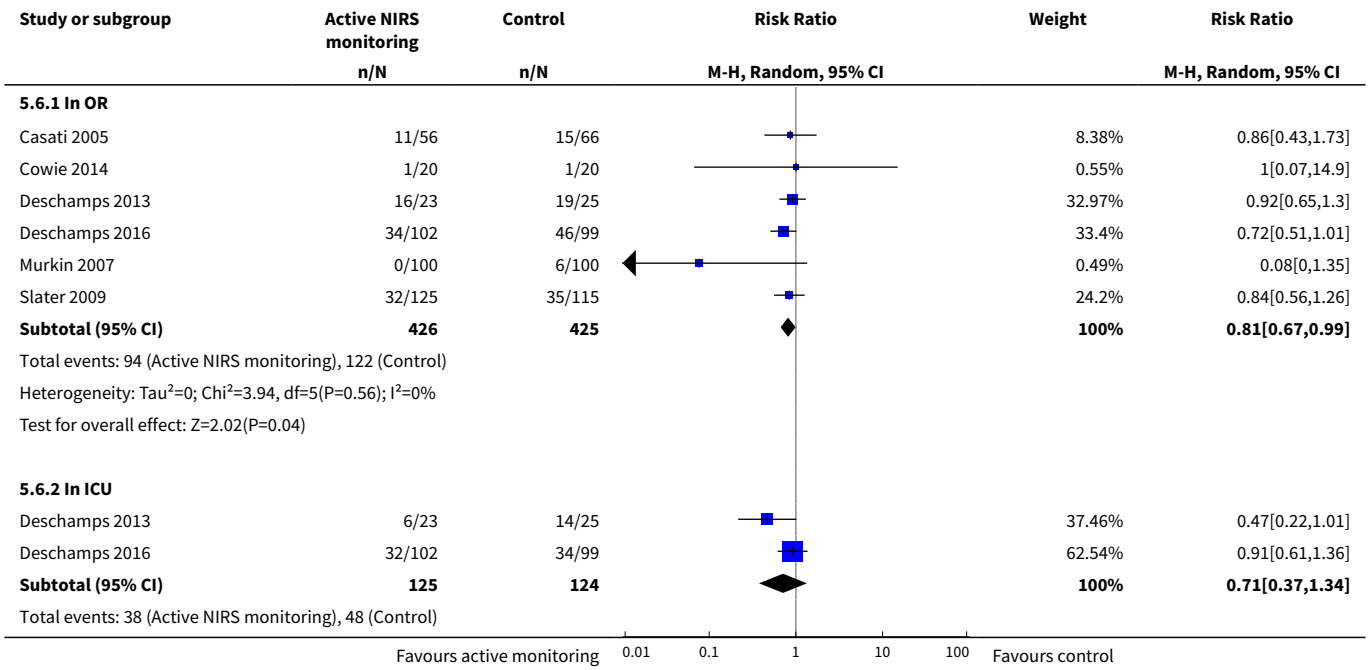




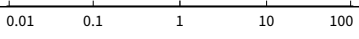
Analysis 5.5. Comparison 5 Sensitivity analysis: missing data, Outcome 5 POCD: decline in cognitive function - 1 week: without missing data.



Analysis 5.6. Comparison 5 Sensitivity analysis: missing data, Outcome 6 Occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: without missing data.



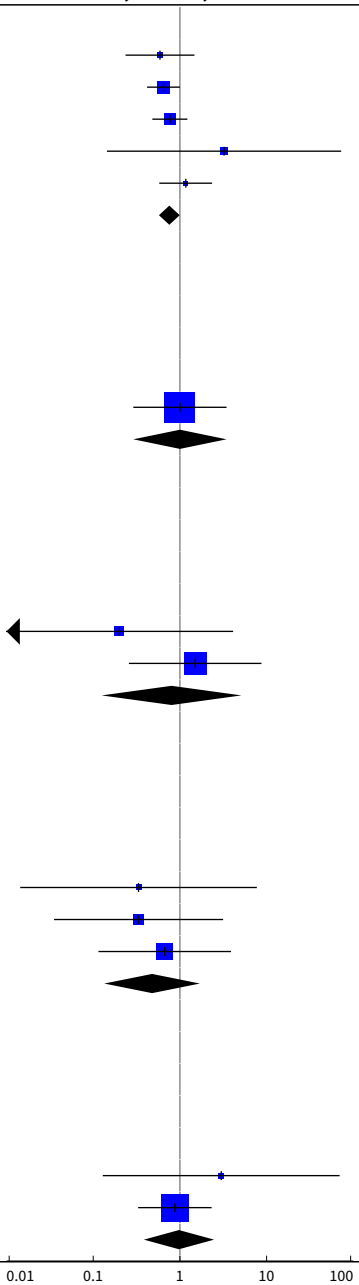
Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.13; Chi²=2.32, df=1(P=0.13); I²=56.95%					
Test for overall effect: Z=1.05(P=0.29)					



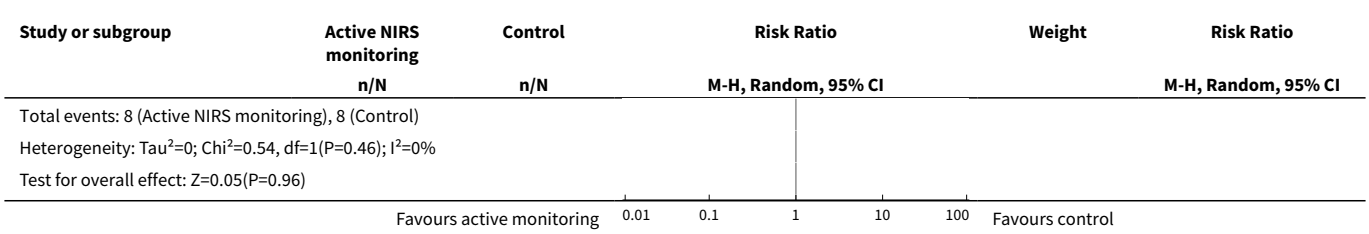
Favours active monitoring — Favours control

Analysis 5.7. Comparison 5 Sensitivity analysis: missing data, Outcome 7 Any major non-neurological complications as defined by individual study: without missing data.

Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.7.1 Non-specific any reported complications					
Casati 2005	6/56	12/66		9.12%	0.59[0.24,1.47]
Cowie 2014	11/20	17/20		39.8%	0.65[0.42,1]
Murkin 2007	23/100	30/100		34.84%	0.77[0.48,1.22]
Trafidlo 2015	1/12	0/13		0.79%	3.23[0.14,72.46]
Vretzakis 2013	14/75	12/75		15.45%	1.17[0.58,2.35]
Subtotal (95% CI)	**263**	**274**		**100%**	**0.76[0.57,0.99]**
Total events: 55 (Active NIRS monitoring), 71 (Control)					
Heterogeneity: Tau²=0; Chi²=3.22, df=4(P=0.52); I²=0%					
Test for overall effect: Z=2(P=0.05)					
5.7.2 Non-specific respiratory complications					
Cowie 2014	4/20	4/20		100%	1[0.29,3.45]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.29,3.45]**
Total events: 4 (Active NIRS monitoring), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.7.3 Arrhythmia					
Murkin 2007	0/100	2/100		31.15%	0.2[0.01,4.11]
Vretzakis 2013	3/75	2/75		68.85%	1.5[0.26,8.72]
Subtotal (95% CI)	**175**	**175**		**100%**	**0.8[0.13,5.12]**
Total events: 3 (Active NIRS monitoring), 4 (Control)					
Heterogeneity: Tau²=0.49; Chi²=1.31, df=1(P=0.25); I²=23.65%					
Test for overall effect: Z=0.23(P=0.81)					
5.7.4 Myocardial infarction					
Cowie 2014	0/20	1/20		16.27%	0.33[0.01,7.72]
Murkin 2007	1/100	3/100		31.86%	0.33[0.04,3.15]
Vretzakis 2013	2/75	3/75		51.87%	0.67[0.11,3.88]
Subtotal (95% CI)	**195**	**195**		**100%**	**0.48[0.13,1.7]**
Total events: 3 (Active NIRS monitoring), 7 (Control)					
Heterogeneity: Tau²=0; Chi²=0.29, df=2(P=0.87); I²=0%					
Test for overall effect: Z=1.14(P=0.25)					
5.7.5 Wound infection					
Cowie 2014	1/20	0/20		8.79%	3[0.13,69.52]
Murkin 2007	7/100	8/100		91.21%	0.88[0.33,2.32]
Subtotal (95% CI)	**120**	**120**		**100%**	**0.98[0.38,2.48]**



Favours active monitoring — Favours control



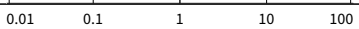
Comparison 6. Sensitivity analysis: reporting bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any major non-neurological complications as defined by individual study: including studies with reporting bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Non-specific any reported complications	6	562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
1.2 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
1.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
1.4 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
1.5 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
1.6 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
1.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]
2 Any major non-neurological complications as defined by individual study: including studies without reporting bias	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Non-specific any reported complications	5	537	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 0.99]
2.2 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]
2.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
2.4 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]

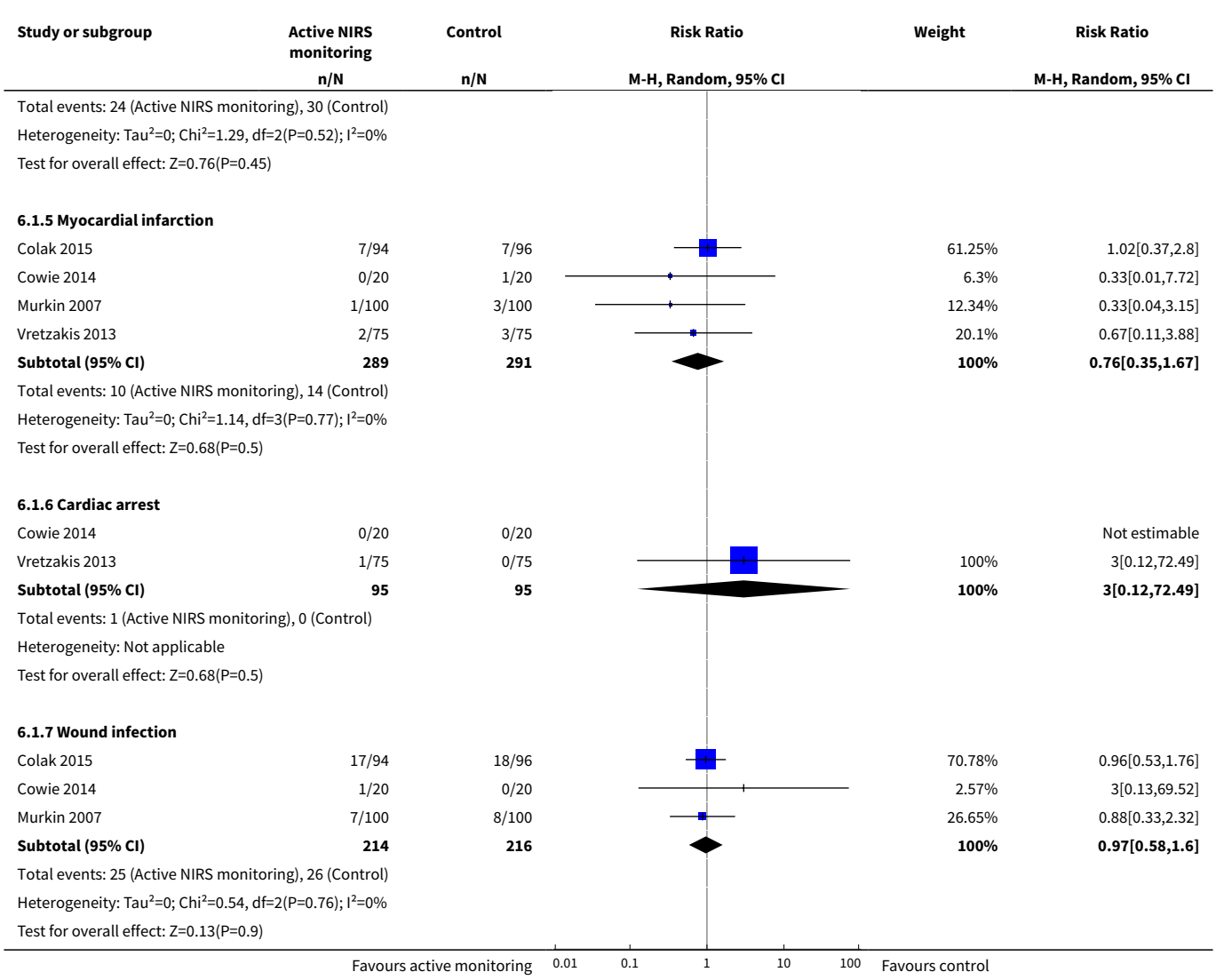
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
2.6 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
2.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]

Analysis 6.1. Comparison 6 Sensitivity analysis: reporting bias, Outcome 1 Any major non-neurological complications as defined by individual study: including studies with reporting bias.

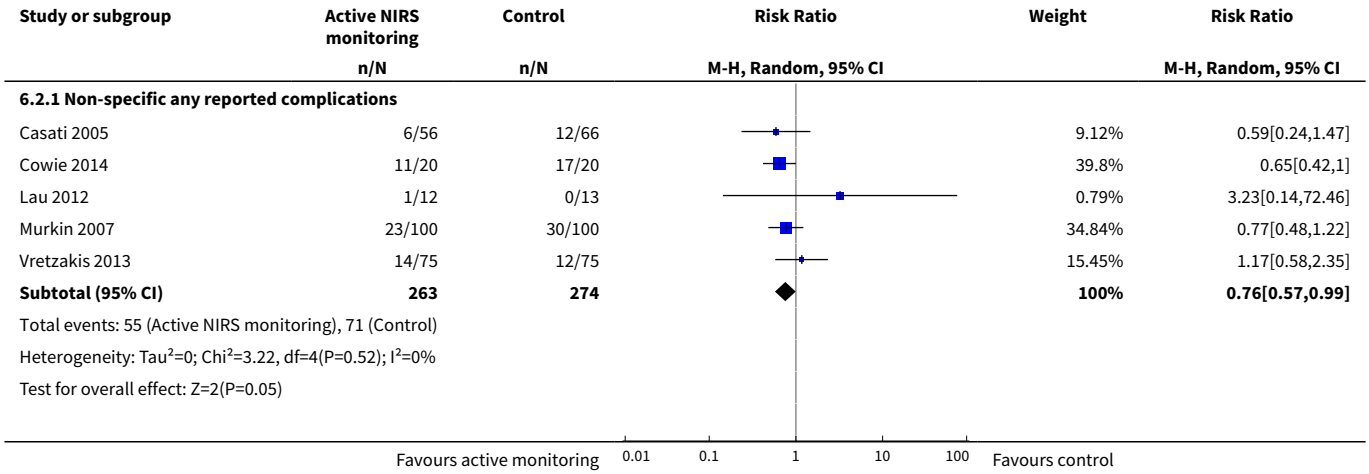
Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Non-specific any reported complications					
Casati 2005	6/56	12/66		9.05%	0.59[0.24,1.47]
Cowie 2014	11/20	17/20		39.49%	0.65[0.42,1]
Lau 2012	1/12	0/13		0.78%	3.23[0.14,72.46]
Murkin 2007	23/100	30/100		34.57%	0.77[0.48,1.22]
Trafidlo 2015	1/12	0/13		0.78%	3.23[0.14,72.46]
Vretzakis 2013	14/75	12/75		15.33%	1.17[0.58,2.35]
Subtotal (95% CI)	**275**	**287**		**100%**	**0.76[0.58,1]**
Total events: 56 (Active NIRS monitoring), 71 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.1, df=5(P=0.53); I^2=0%					
Test for overall effect: Z=1.92(P=0.05)					
6.1.2 Non-specific cardiac complications					
Casati 2005	1/56	1/66		14.01%	1.18[0.08,18.41]
Murkin 2007	1/100	5/100		22.49%	0.2[0.02,1.68]
Vretzakis 2013	6/75	5/75		63.51%	1.2[0.38,3.76]
Subtotal (95% CI)	**231**	**241**		**100%**	**0.8[0.28,2.31]**
Total events: 8 (Active NIRS monitoring), 11 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=2.25, df=2(P=0.33); I^2=11.02%					
Test for overall effect: Z=0.41(P=0.68)					
6.1.3 Non-specific renal complications					
Colak 2015	0/94	1/96		13.13%	0.34[0.01,8.25]
Cowie 2014	4/20	4/20		86.87%	1[0.29,3.45]
Subtotal (95% CI)	**114**	**116**		**100%**	**0.87[0.27,2.76]**
Total events: 4 (Active NIRS monitoring), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					
6.1.4 Arrhythmia					
Colak 2015	21/94	26/96		90.26%	0.82[0.5,1.36]
Murkin 2007	0/100	2/100		2.47%	0.2[0.01,4.11]
Vretzakis 2013	3/75	2/75		7.28%	1.5[0.26,8.72]
Subtotal (95% CI)	**269**	**271**		**100%**	**0.83[0.52,1.34]**

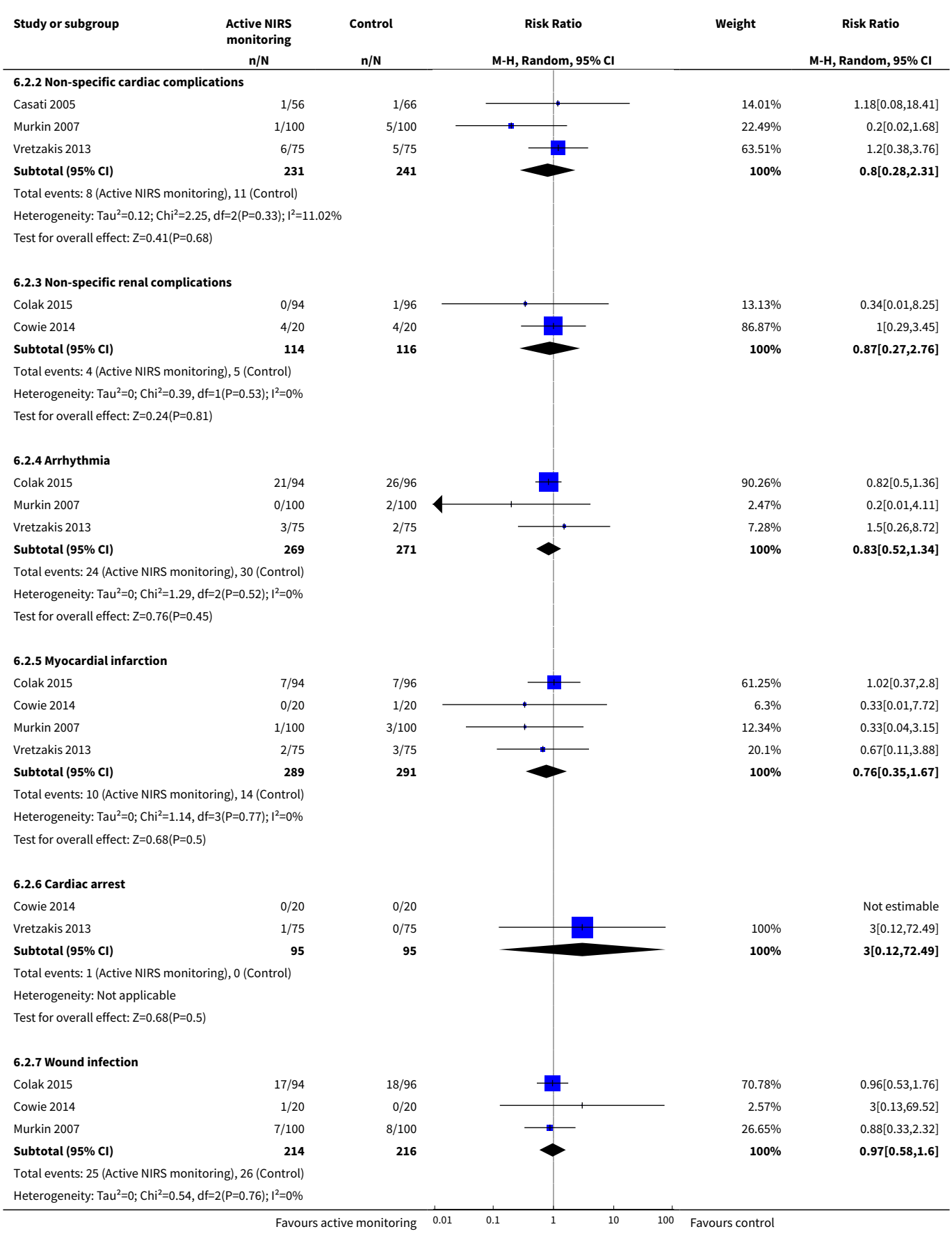


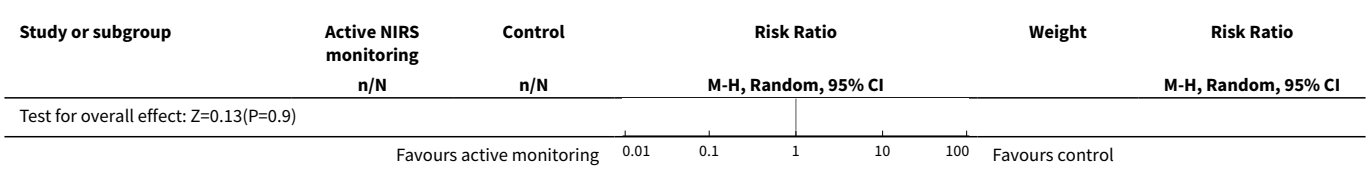
Favours active monitoring — Favours control



Analysis 6.2. Comparison 6 Sensitivity analysis: reporting bias, Outcome 2 Any major non-neurological complications as defined by individual study: including studies without reporting bias.







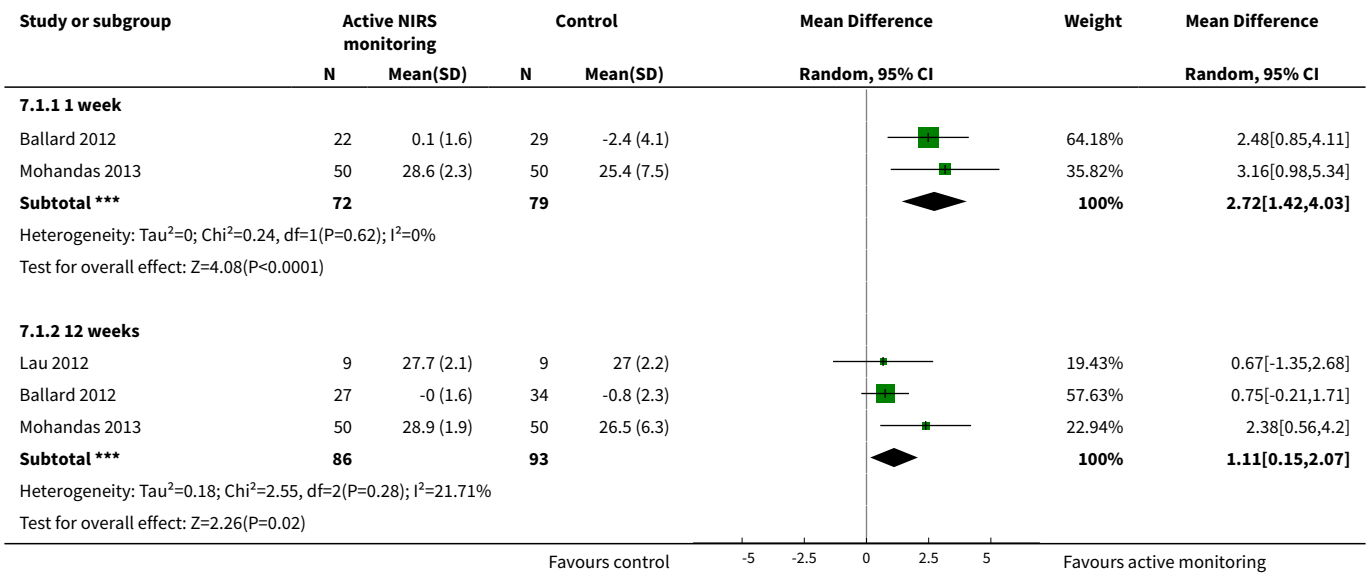
Comparison 7. Sensitivity analysis: other bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies with other bias	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 week	2	151	Mean Difference (IV, Random, 95% CI)	2.72 [1.42, 4.03]
1.2 12 weeks	3	179	Mean Difference (IV, Random, 95% CI)	1.11 [0.15, 2.07]
2 POCD defined by original studies - 1 week: including studies with other bias	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mild	2	126	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.30, 0.95]
2.2 Severe	2	126	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.03, 0.92]
3 Intraoperative mortality or postoperative mortality: Death: including studies with other bias	3	390	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.08, 5.03]
4 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies with other bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 In OR	7	916	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
4.2 In ICU	2	249	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.34]
5 Any major non-neurological complications as defined by individual study: including studies with other bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Non-specific any reported complications	6	562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
5.2 Non-specific cardiac complications	3	472	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.31]

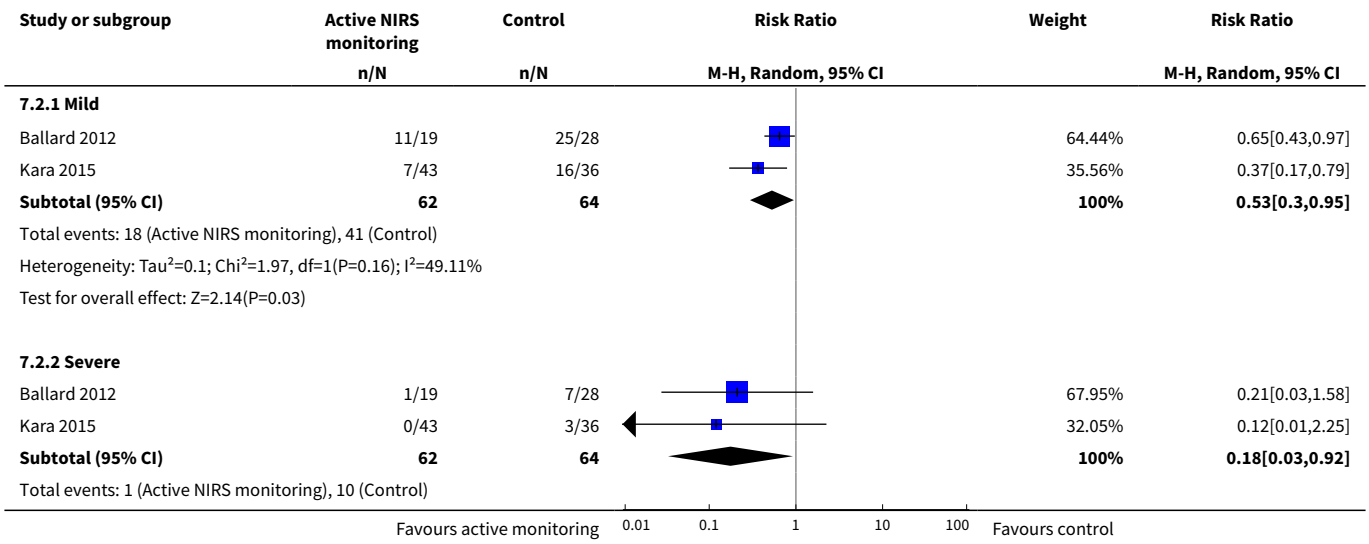
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Non-specific renal complications	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.76]
5.4 Arrhythmia	3	540	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
5.5 Myocardial infarction	4	580	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.35, 1.67]
5.6 Cardiac arrest	2	190	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]
5.7 Wound infection	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.60]
6 Length of ICU stay (days): including studies with other bias	3	379	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.48, -0.09]
7 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies without other bias	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 12 weeks	2	118	Mean Difference (IV, Random, 95% CI)	1.58 [-0.10, 3.25]
8 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies without other bias	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 In OR	3	410	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.13]
9 Any major non-neurological complications as defined by individual study: including studies without other bias	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Non-specific any reported complications	4	322	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.57, 1.68]
9.2 Non-specific cardiac complications	2	272	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.42, 3.44]
9.3 Non-specific renal complications	1	190	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.25]
9.4 Arrhythmia	2	340	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.53, 1.39]
9.5 Myocardial infarction	2	340	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.38, 2.20]
9.6 Cardiac arrest	1	150	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.49]

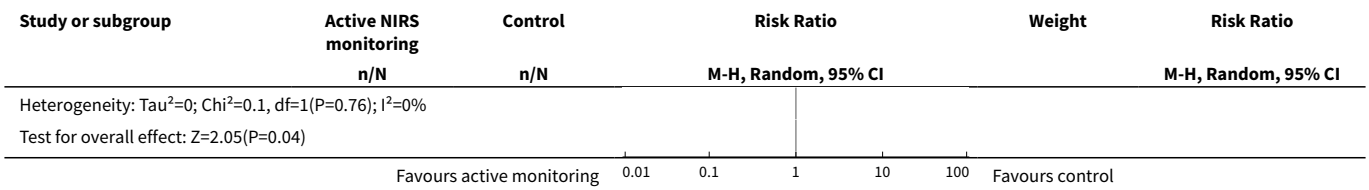
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.7 Wound infection	1	190	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.53, 1.76]
10 Length of ICU stay (days): including studies without other bias	2	179	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.39, -0.07]

Analysis 7.1. Comparison 7 Sensitivity analysis: other bias, Outcome 1 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies with other bias.

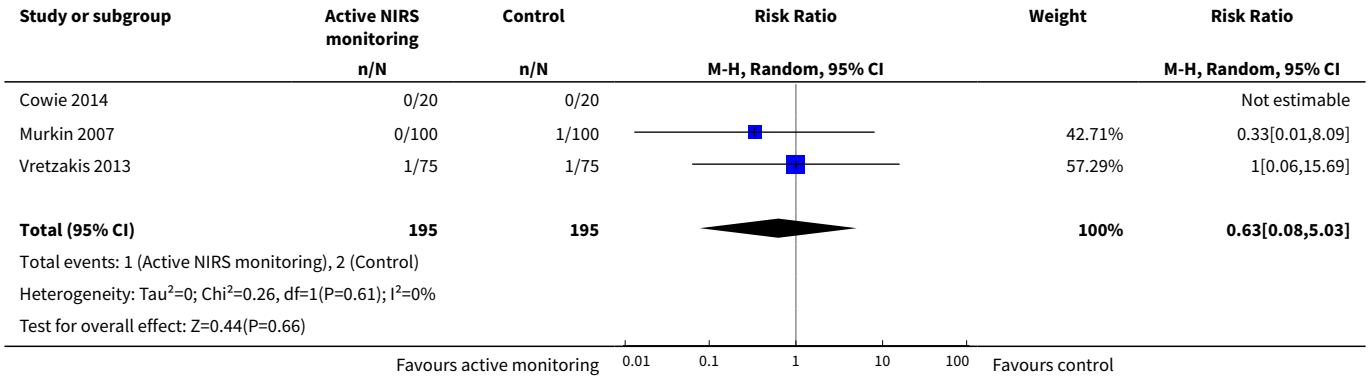


Analysis 7.2. Comparison 7 Sensitivity analysis: other bias, Outcome 2 POCD defined by original studies - 1 week: including studies with other bias.

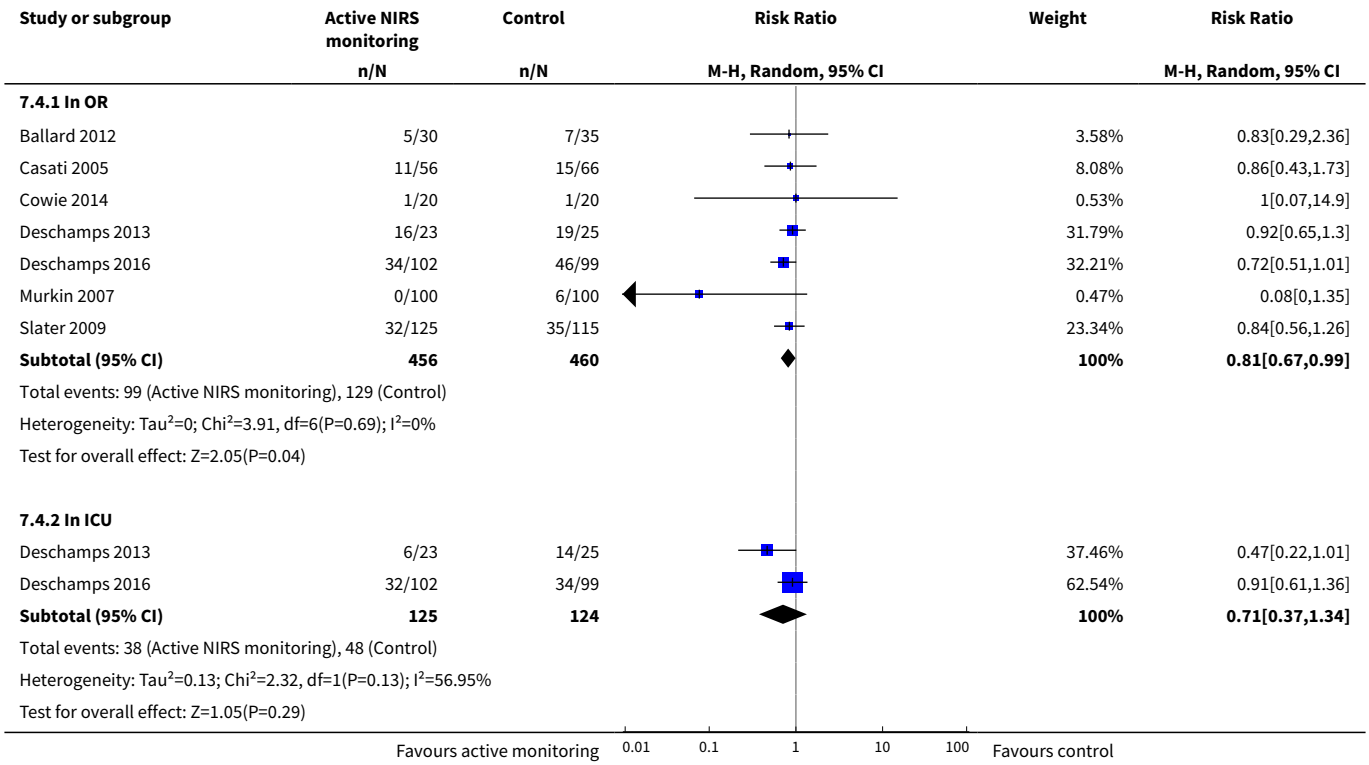




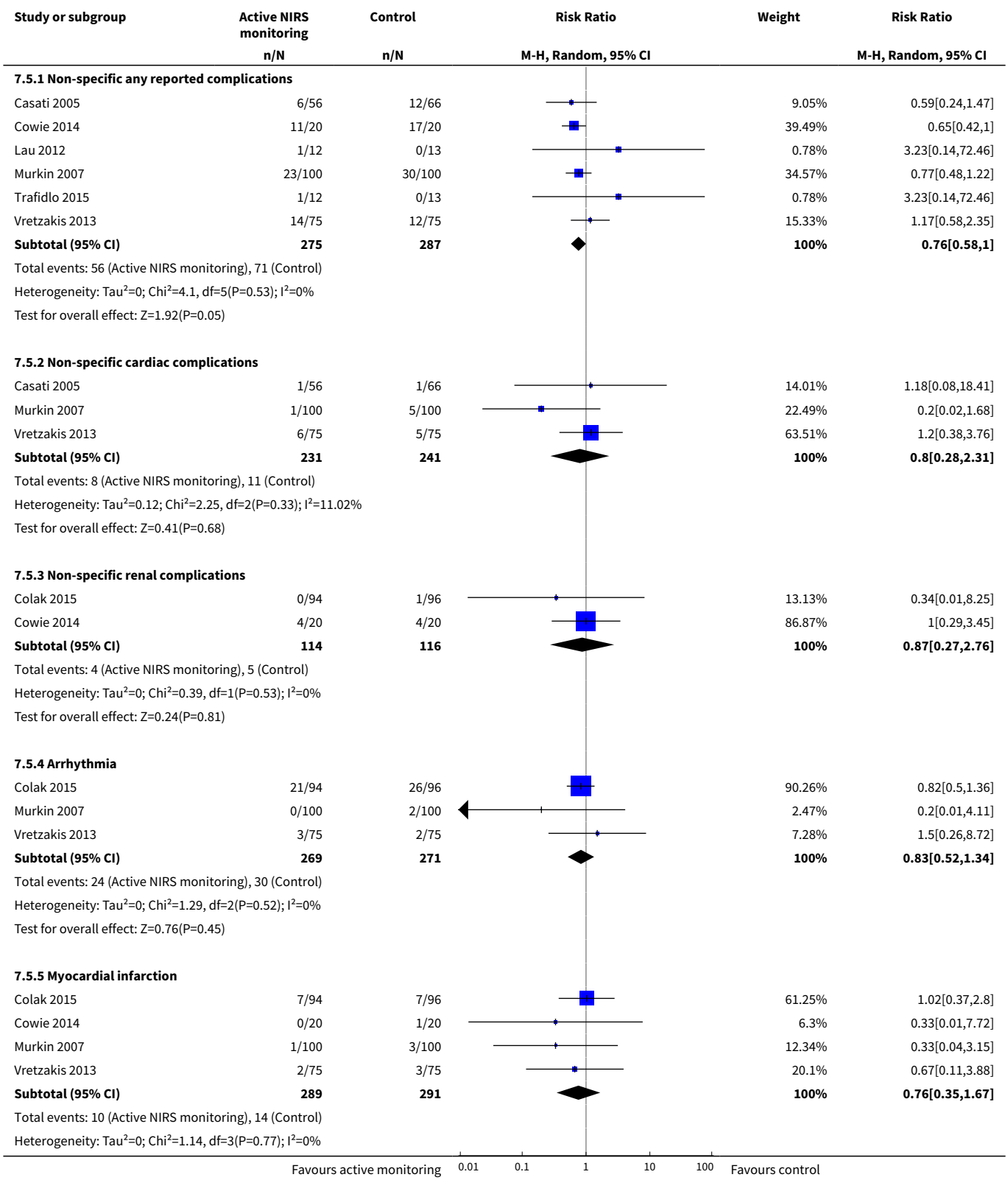
Analysis 7.3. Comparison 7 Sensitivity analysis: other bias, Outcome 3 Intraoperative mortality or postoperative mortality: Death: including studies with other bias.

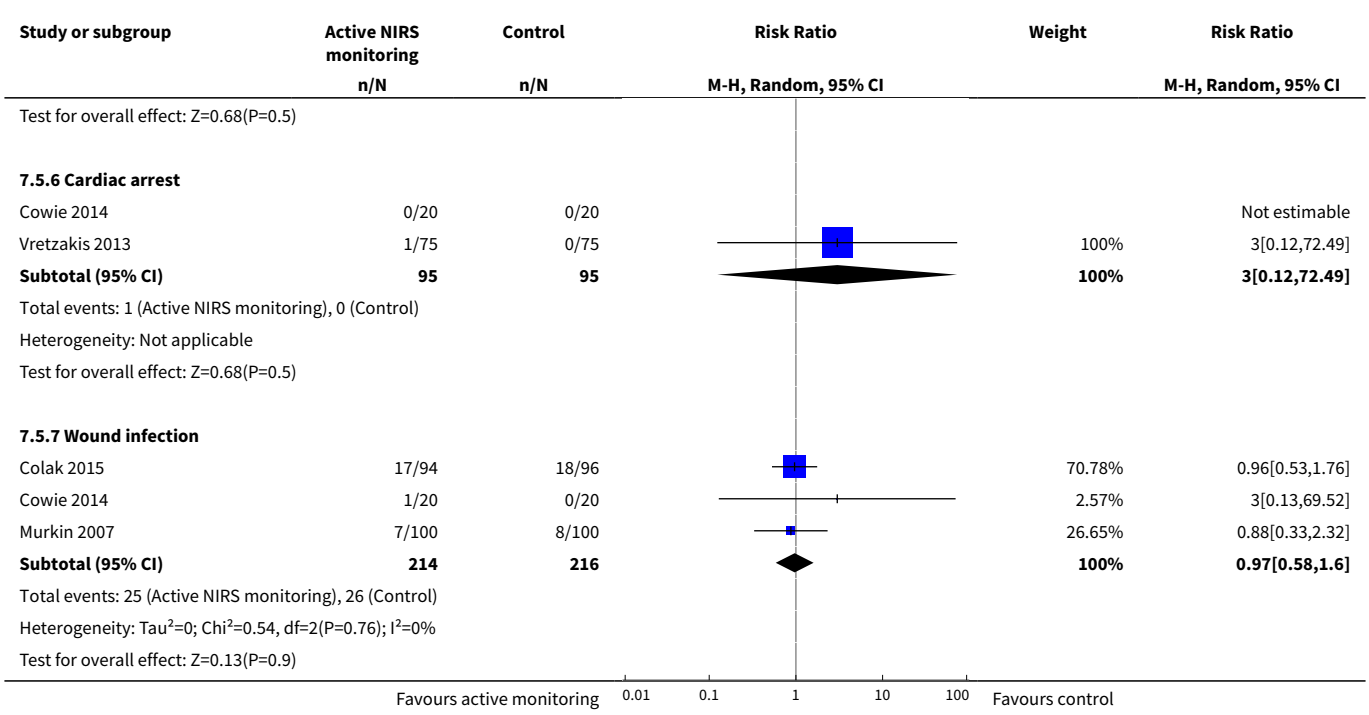


Analysis 7.4. Comparison 7 Sensitivity analysis: other bias, Outcome 4 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies with other bias.

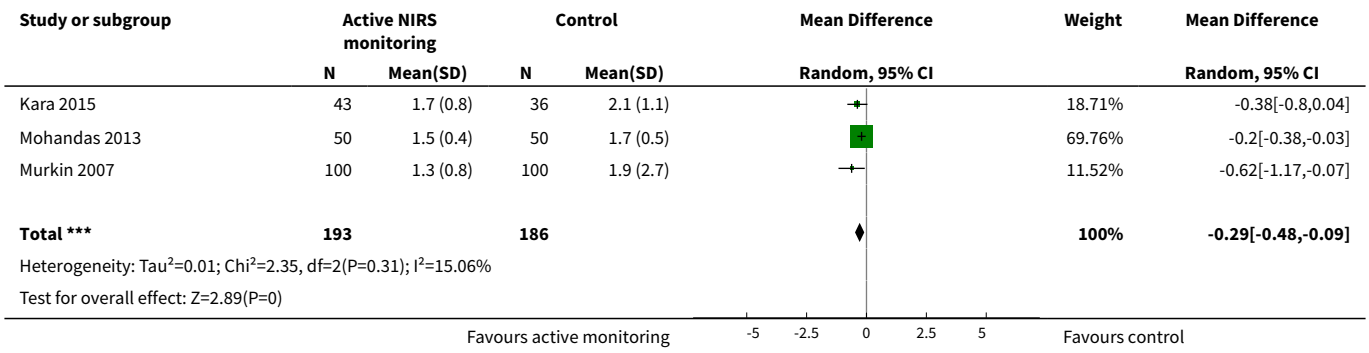


Analysis 7.5. Comparison 7 Sensitivity analysis: other bias, Outcome 5 Any major non-neurological complications as defined by individual study: including studies with other bias.

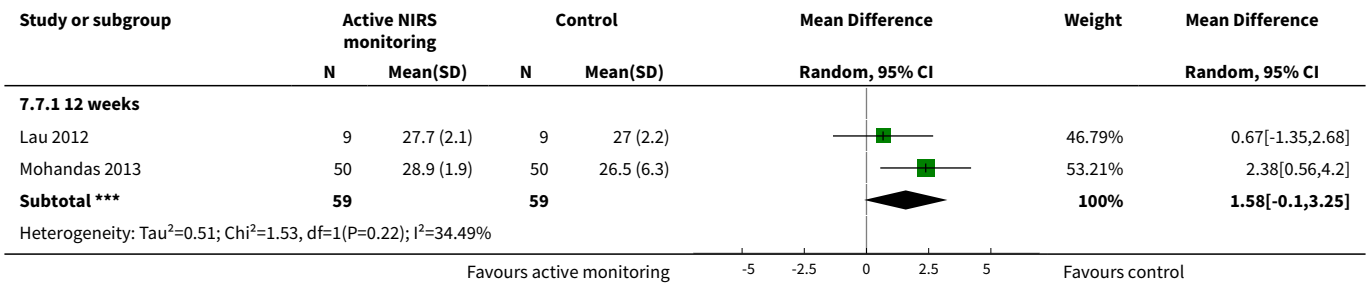




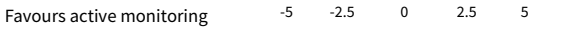
Analysis 7.6. Comparison 7 Sensitivity analysis: other bias, Outcome 6 Length of ICU stay (days): including studies with other bias.



Analysis 7.7. Comparison 7 Sensitivity analysis: other bias, Outcome 7 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies without other bias.

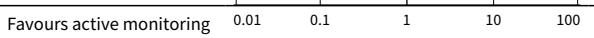


Study or subgroup	Active NIRS monitoring N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.85(P=0.06)							



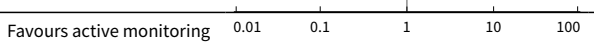
Analysis 7.8. Comparison 7 Sensitivity analysis: other bias, Outcome 8 The occurrence of abnormal $rScO_2$ during or after surgery: Desaturation: including studies without other bias.

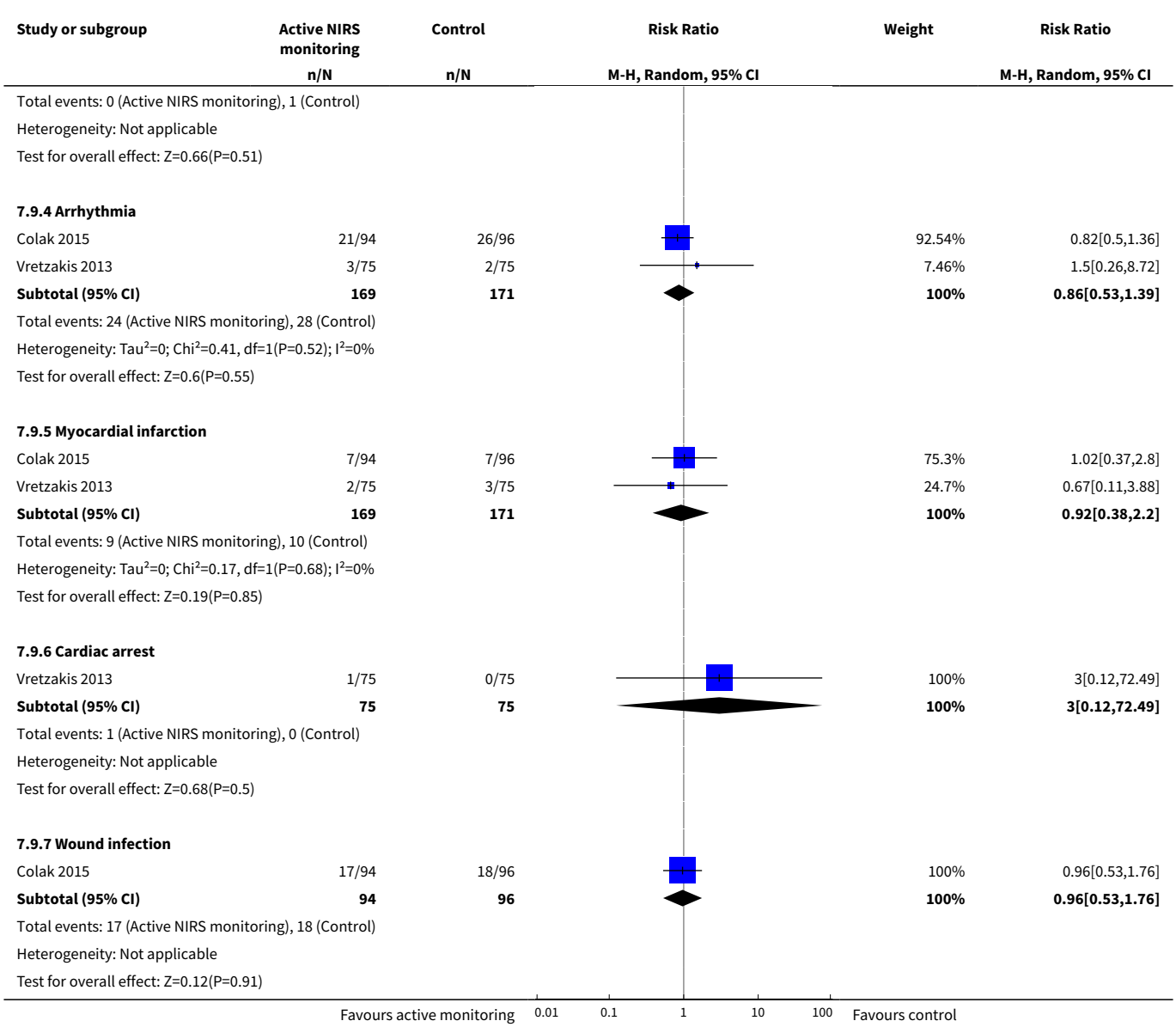
Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.8.1 In OR					
Casati 2005	11/56	15/66		12.78%	0.86[0.43,1.73]
Deschamps 2013	16/23	19/25		50.3%	0.92[0.65,1.3]
Slater 2009	32/125	35/115		36.92%	0.84[0.56,1.26]
Subtotal (95% CI)	**204**	**206**		**100%**	**0.88[0.69,1.13]**
Total events: 59 (Active NIRS monitoring), 69 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.12$, df=2(P=0.94); $I^2=0\%$					
Test for overall effect: Z=1.01(P=0.31)					



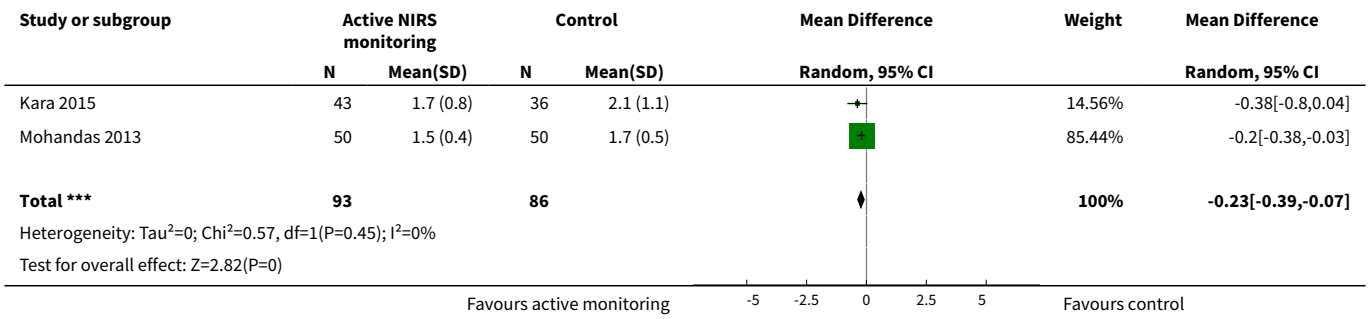
Analysis 7.9. Comparison 7 Sensitivity analysis: other bias, Outcome 9 Any major non-neurological complications as defined by individual study: including studies without other bias.

Study or subgroup	Active NIRS monitoring n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.9.1 Non-specific any reported complications					
Casati 2005	6/56	12/66		34.89%	0.59[0.24,1.47]
Lau 2012	1/12	0/13		3.01%	3.23[0.14,72.46]
Trafidlo 2015	1/12	0/13		3.01%	3.23[0.14,72.46]
Vretzakis 2013	14/75	12/75		59.1%	1.17[0.58,2.35]
Subtotal (95% CI)	**155**	**167**		**100%**	**0.98[0.57,1.68]**
Total events: 22 (Active NIRS monitoring), 24 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.56$, df=3(P=0.46); $I^2=0\%$					
Test for overall effect: Z=0.08(P=0.93)					
7.9.2 Non-specific cardiac complications					
Casati 2005	1/56	1/66		14.74%	1.18[0.08,18.41]
Vretzakis 2013	6/75	5/75		85.26%	1.2[0.38,3.76]
Subtotal (95% CI)	**131**	**141**		**100%**	**1.2[0.42,3.44]**
Total events: 7 (Active NIRS monitoring), 6 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=1(P=0.99); $I^2=0\%$					
Test for overall effect: Z=0.33(P=0.74)					
7.9.3 Non-specific renal complications					
Colak 2015	0/94	1/96		100%	0.34[0.01,8.25]
Subtotal (95% CI)	**94**	**96**		**100%**	**0.34[0.01,8.25]**





Analysis 7.10. Comparison 7 Sensitivity analysis: other bias, Outcome 10 Length of ICU stay (days): including studies without other bias.



ADDITIONAL TABLES

Table 1. Primary outcomes: single study forest plots and empty forest plots

1 Postoperative stroke or other neurological injury								
1.1 Neurological injury								
	Active NIRS monitoring		Blinded NIRS monitoring		Risk ratio			
	Events	Total	Events	Total	Mantel-Haenszel, fixed-effect model, 95% CI			
Casati 2005	0	56	4	66	0.13 (0.01 to 2.37)			
Colak 2015	4	94	1	96	4.09 (0.47 to 35.88)			
1.2 Stroke								
Cowie 2014	0	20	0	20	Not estimable			
Murkin 2007	1	100	4	100	0.25 (0.03 to 2.20)			
2 Postoperative stroke or other neurological injury: ASEM (endpoint score)								
2.1 1 week								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Mohandas 2013	17.46	1.99	50	15.04	4.8	50	100.0%	2.42 (0.98 to 3.86)
Subtotal (95% CI)			50			50	100.0%	2.42 (0.98 to 3.86)
Test for overall effect: Z = 3.29 (P = 0.0010)								
2.2 12 weeks								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI

Table 1. Primary outcomes: single study forest plots and empty forest plots *(Continued)*

Mohandas 2013	17.68	1.79	50	15.69	3.99	50	100.0%	1.99 (0.78 to 3.20)
Subtotal (95% CI)			50			50	100.0%	1.99 (0.78 to 3.20)
Test for overall effect: Z = 3.22 (P = 0.001)								
3 Postoperative stroke or other neurological injury: Vigilance Reaction Time (change score)								
3.1 1 week								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	6.39	80.9	22	27.95	54.99	29	100.0%	-21.56 (-60.85 to 17.73)
Subtotal (95% CI)			22			29	100.0%	-21.56 (-60.85 to 17.73)
Test for overall effect: Z = 1.08 (P = 0.28)								
3.2 12 weeks								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	-11.73	33.5	27	13.61	29.69	34	100.0%	-25.34 (-41.44 to -9.24)
Subtotal (95% CI)			27			34	100.0%	-25.34 (-41.44 to -9.24)
Test for overall effect: Z = 3.08 (P = 0.002)								
3.3 52 weeks								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference

Table 1. Primary outcomes: single study forest plots and empty forest plots *(Continued)*

	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	-10.8	36.28	28	15.1	40.73	32	100.0%	-25.90 (-45.39 to -6.41)
Subtotal (95% CI)			28			32	100.0%	-25.90 (-45.39 to -6.41)
Test for overall effect: Z = 2.61 (P = 0.009)								
4 Postoperative stroke or other neurological injury: Trail Making (change score)								
4.1 12 weeks								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	-0.23	0.73	27	0.47	1.34	34	100.0%	-0.70 (-1.23 to -0.17)
Subtotal (95% CI)			27			34	100.0%	-0.70 (-1.23 to -0.17)
Test for overall effect: Z = 2.60 (P = 0.009)								
4.2 52 weeks								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	0.12	0.68	28	-0.47	0.93	32	100.0%	0.59 (0.18 to 1.00)
Subtotal (95% CI)			28			32	100.0%	0.59 (0.18 to 1.00)
Test for overall effect: Z = 2.83 (P = 0.005)								
5 POD: postoperative delirium								

Table 1. Primary outcomes: single study forest plots and empty forest plots *(Continued)*

	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Colak 2015	8	94	13	96	100.0%	0.63 (0.27 to 1.45)
Total (95% CI)		94		96	100.0%	0.63 (0.27 to 1.45)
Total events	8		13			
Test for overall effect: Z = 1.09 (P = 0.27)						
6 POCD as defined by the original studies - 12 weeks						
6.1 Mild						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	13	24	27	33	100.0%	0.66 (0.44 to 0.99)
Subtotal (95% CI)		24		33	100.0%	0.66 (0.44 to 0.99)
Total events	13		27			
Test for overall effect: Z = 2.01 (P = 0.04)						
6.2 Moderate						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	6	24	9	33	100.0%	0.92 (0.38 to 2.23)
Subtotal (95% CI)		24		33	100.0%	0.92 (0.38 to 2.23)
Total events	6		9			

Table 1. Primary outcomes: single study forest plots and empty forest plots *(Continued)*

Test for overall effect: Z = 0.19 (P = 0.85)						
6.3 Severe						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	2	24	4	33	100.0%	0.69 (0.14 to 3.45)
Subtotal (95% CI)		24		33	100.0%	0.69 (0.14 to 3.45)
Total events	2		4			
Test for overall effect: Z = 0.46 (P = 0.65)						
7 POCD as defined by the original studies - 52 weeks						
7.1 Mild						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	15	27	27	32	100.0%	0.66 (0.46 to 0.95)
Subtotal (95% CI)		27		32	100.0%	0.66 (0.46 to 0.95)
Total events	15		27			
Test for overall effect: Z = 2.22 (P = 0.03)						
7.2 Moderate						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	3	27	12	32	100.0%	0.30 (0.09 to 0.94)

Table 1. Primary outcomes: single study forest plots and empty forest plots *(Continued)*

Subtotal (95% CI)		27		32	100.0%	0.30 (0.09 to 0.94)
Total events	3		12			
Test for overall effect: Z = 2.06 (P = 0.04)						
7.3 Severe						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	1	27	4	32	100.0%	0.30 (0.04 to 2.49)
Subtotal (95% CI)		27		32	100.0%	0.30 (0.04 to 2.49)
Total events	1		4			
Test for overall effect: Z = 1.12 (P = 0.26)						

ASEM: antisaccadic eye movement test; CI: confidence interval; IQR: interquartile range; N: number; NIRS: near-infrared spectroscopy; POCD: postoperative cognitive dysfunction; POD: postoperative delirium; S100B: one biomarker of cerebral damage; SD: standard deviation

Table 2. Secondary outcomes: single study forest plots and empty forest plots

1 The occurrence of abnormal $rScO_2$ during or after surgery: desaturation time								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Harilall 2014	24.7	11.819	20	63.85	23.424	20	100.0%	-39.15 (-50.65 to -27.65)
Total (95% CI)			20			20	100.0%	-39.15 (-50.65 to -27.65)
Test for overall effect: Z = 6.67 (P < 0.00001)								
2 The occurrence of abnormal $rScO_2$ during or after surgery: $rScO_2$ below 50%								

Table 2. Secondary outcomes: single study forest plots and empty forest plots *(Continued)*

	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Ballard 2012	1	30	6	35	100.0%	0.19 (0.02 to 1.53)
Total (95% CI)		30		35	100.0%	0.19 (0.02 to 1.53)
Total events	1		6			
Test for overall effect: Z = 1.56 (P = 0.12)						

3 Length of hospital stay (days)

	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Kara 2015	7.15	1.39	43	7.67	1.14	36	100.0%	-0.52 (-1.08 to 0.04)
Total (95% CI)			43			36	100.0%	-0.52 (-1.08 to 0.04
Test for overall effect: Z = 1.83 (P = 0.07)								

4 Length of hospital stay (days)

Study ID	Group	Mean	SD/95% CI	N
Cowie 2014	Intervention group	7.9	4.8 to 10.9	20
	Control group	10.6	5.5 to 15.8	20
Deschamps 2013	Intervention group	7.6	5.4	23
	Control group	7.9	3.2	25
Murkin 2007	Intervention group	6.1	4.4	100

Table 2. Secondary outcomes: single study forest plots and empty forest plots *(Continued)*

	Control group	6.9	5.5	100
Vretzakis 2013	Intervention group	10.9	3.6	75
	Control group	10.2	10.7	75

CI: confidence interval; N: number; NIRS: near-infrared spectroscopy; $rScO_2$: regional cerebral oxygen saturation; SD: standard deviation

Table 3. Sensitivity analysis: missing data - single study forest plots and empty forest plots

1 Postoperative stroke or other neurological injury: including studies with missing data

1.1 Neurological injury

	Active NIRS monitoring		Blinded NIRS monitoring		Risk ratio
	Events	Total	Events	Total	Mantel-Haenszel, fixed-effect model, 95% CI
Casati 2005	0	56	4	66	0.13 (0.01 to 2.37)
Colak 2015	4	94	1	96	4.09 (0.47 to 35.88)
1.2 Stroke					
Cowie 2014	0	20	0	20	Not estimable
Murkin 2007	1	100	4	100	0.25 (0.03 to 2.20)

2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies with missing data

2.1 52 weeks

	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Ballard 2012	0.69	1.47	28	-0.94	2.18	32	100.0%	1.63 (0.70 to 2.56)
Subtotal (95% CI)			28			32	100.0%	1.63 (0.70 to 2.56)

Table 3. Sensitivity analysis: missing data - single study forest plots and empty forest plots *(Continued)*

Test for overall effect: Z = 3.43
(P = 0.0006)

3 Postoperative stroke or other neurological injury: without missing data								
3.1 Neurological injury								
	Active NIRS monitoring		Blinded NIRS monitoring		Risk ratio			
	Events	Total	Events	Total	Mantel-Haenszel, fixed-effect model, 95% CI			
Casati 2005	0	56	4	66	0.13 (0.01 to 2.37)			
3.2 Stroke								
Cowie 2014	0	20	0	20	Not estimable			
Murkin 2007	1	100	4	100	0.25 (0.03 to 2.20)			
4 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): without missing data								
4.1 1 week								
	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Mohandas 2013	28.58	2.29	50	25.42	7.54	50	100.0%	3.16 (0.98 to 5.34)
Subtotal (95% CI)			50			50	100.0%	3.16 (0.98 to 5.34)
Test for overall effect: Z = 2.84 (P = 0.005)								
65.2 12 weeks								
Mohandas 2013	28.88	1.88	50	26.5	6.31	50	100.0%	2.38 (0.56 to 4.20)
Subtotal (95% CI)			50			50	100.0%	2.38 (0.56 to 4.20)

Table 3. Sensitivity analysis: missing data - single study forest plots and empty forest plots *(Continued)*

Test for overall effect: Z = 2.56
(P = 0.01)

CI: confidence interval; MMSE: mini-mental state examination; NIRS: near-infrared spectroscopy; SD: standard deviation

Table 4. Sensitivity analysis: other bias - single study forest plots

1 POCD defined by original studies - 1 week: including studies without other bias						
1.1 Mild						
	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Kara 2015	7	43	16	36	100.0%	0.37 (0.17 to 0.79)
Subtotal (95% CI)		43		36	100.0%	0.37 (0.17 to 0.79)
Total events	7		16			
Heterogeneity: not applicable						
Test for overall effect: Z = 2.56 (P = 0.01)						
1.2 Severe						
Kara 2015	0	43	3	36	100.0%	0.12 (0.01 to 2.25)
Subtotal (95% CI)		43		36	100.0%	0.12 (0.01 to 2.25)
Total events	0		3			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
2 Postoperative stroke or other neurological injury: MMSE (endpoint or change score): including studies without other bias						
2.1 1 week						

Table 4. Sensitivity analysis: other bias - single study forest plots *(Continued)*

	Active NIRS monitoring			Blinded NIRS monitoring			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		Inverse variance, fixed-effect model, 95% CI
Mohandas 2013	28.58	2.29	50	25.42	7.54	50	100.0%	3.16 (0.98 to 5.34)
Subtotal (95% CI)			50			50	100.0%	3.16 (0.98 to 5.34)
Test for overall effect: Z = 2.84 (P = 0.005)								

3 Intraoperative mortality or postoperative mortality: death: including studies without other bias

	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Vretzakis 2013	1	75	1	75	100.0%	1.00 (0.06 to 15.69)
Total (95% CI)		75		75	100.0%	1.00 (0.06 to 15.69)
Total events	1		1			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

4 The occurrence of abnormal $rScO_2$ during or after surgery: desaturation: including studies without other bias

4.1 In ICU

	Active NIRS monitoring		Blinded NIRS monitoring		Weight	Risk ratio
	Events	Total	Events	Total		Mantel-Haenszel, fixed-effect model, 95% CI
Deschamps 2013	6	23	14	25	100.0%	0.47 (0.22 to 1.01)
Subtotal (95% CI)		23		25	100.0%	0.47 (0.22 to 1.01)
Total events	6		14			

Table 4. Sensitivity analysis: other bias - single study forest plots *(Continued)*

Heterogeneity: not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

CI: confidence interval; ICU: intensive care unit; MMSE: mini-mental state examination; NIRS: near-infrared spectroscopy; POCD: postoperative cognitive dysfunction; SD: standard deviation; $rScO_2$: regional cerebral oxygen saturation

APPENDICES

Appendix 1. CENTRAL search strategy

#1 head or crania* or craniocerebral or capitis or craniu* or cerebra* or cerebru* or brain* or forebrain* or skull* or hemispher* or intracran* or encephal*:ti,ab,kw

#2 (oxygen saturation*) or oximetr* or oxygenati* or ScO2:ti,ab,kw

#3 MeSH descriptor: [Oximetry] explode all trees

#4 #2 or #3

#5 #1 and #4

#6 (near-infrared spectromet*) or (near-infrared spectroscop*) or (spectroscop*, near-infrared) or (NIR spectroscop*) or (spectroscop*, NIR) or (spectromet*, near-infrared)

#7 MeSH descriptor: [Spectroscopy, Near-Infrared] explode all trees

#8 #5 or #6 or #7

#9 operati* or perioperat* or peroperat* or preoperati* or postoperat* or intraoperat* or surg* or (anesthe* recovery)

#10 MeSH descriptor: [Perioperative Care] explode all trees

#11 MeSH descriptor: [Perioperative Nursing] explode all trees

#12 MeSH descriptor: [Specialties, Surgical] explode all trees

#13 #9 or #10 or #11 or #12

#14 #8 and #13

#15 MeSH descriptor: [Models, Animal] explode all trees

#16 MeSH descriptor: [Animals] explode all trees

#17 MeSH descriptor: [Animal Experimentation] explode all trees

#18 MeSH descriptor: [Disease Models, Animal] explode all trees

#19 MeSH descriptor: [Animals, Laboratory] explode all trees

#20 MeSH descriptor: [Humans] explode all trees

#21 MeSH descriptor: [Infant, Newborn] explode all trees

#22 (newborn infant*) or newborn* or neonate*:ti,ab,kw

#23 #15 or #16 or #17 or #18 or #19

#24 #21 or #22

#25 #23 not #20

#26 #14 not #25

#27 #26 not #24

Appendix 2. Embase search strategy

#1 'head'/exp OR head OR crania* OR craniocerebral OR capitis OR craniu* OR cerebra* OR cerebru* OR brain* OR forebrain* OR skull* OR hemispher* OR intracran* OR encephal*:ab,ti

#2 oxygen NEAR/3 saturation* OR oximetr* OR oxygenati* OR sco2:ab,ti

#3 'oximetry'/exp

#4 #2 OR #3

#5 #1 AND #4

#6 'near infrared spectroscopy'/exp

#7 (near-infrared AND spectromet*) OR (near-infrared AND spectroscop*) OR (NIR AND spectroscop*):ab,ti

#8 #5 OR #6 OR #7

#9 operati* OR perioperat* OR peroperat* OR preoperati* OR postoperat* OR intraoperat* OR surg* OR (anesthe* NEAR/3 recovery):ab,ti

#10 'perioperative period'/exp

#11 'perioperative nursing'/exp

#12 'perioperative complication'/exp

#13 'surgery'/exp

#14 #9 OR #10 OR #11 OR #12 OR #13

#15 'randomized controlled trial'/exp

#16 'randomized controlled trial' OR 'randomized controlled trial':ab,ti

#17 random*:ab,ti

#18 'randomization'/exp

#19 'controlled clinical trial'/exp

#20 'clinical trial'/exp

#21 'multicenter study'/exp

#22 multicent*:ab,ti

#23 'phase 4 clinical trial'/exp

#24 'double blind procedure'/exp

#25 'single blind procedure'/exp

#26 random* OR cross?over* OR factorial* OR placebo* OR volunteer*:ab,ti

#27 singl*:ab,ti OR doubl*:ab,ti OR trebl*:ab,ti OR tripl*:ab,ti AND (blind*:ab,ti OR mask*:ab,ti)

#28 randomized:ab,ti OR randomized:ab,ti OR randomly:ab,ti OR 'random order':ab,ti OR 'random sequence':ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'at random':ab,ti OR 'randomized controlled trial':ab,ti OR 'controlled clinical trial':ab,ti

#29 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#30 'human'/exp

#31 'animal'/exp OR 'nonhuman'/exp OR 'experimental animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'disease model'/exp

#32 rat*:ab,ti OR rodent*:ab,ti OR animal*:ab,ti OR mice:ab,ti OR murin*:ab,ti OR dog*:ab,ti OR canine*:ab,ti OR cat*:ab,ti OR feline*:ab,ti OR rabbit*:ab,ti OR pig*:ab,ti

#33 'newborn'/exp

#34 newborn NEAR/3 infant* OR newborn* or neonate*:ab,ti

#35 #33 OR #34

#36 #31 OR #32

#37 #36 NOT #30

#38 #29 NOT #37

#39 #38 NOT #35

#40 #8 AND #14 AND #39

Appendix 3. MEDLINE (PubMed) search strategy

#1 (randomized or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or randomized controlled trial)[pt]

#2 controlled clinical trial[pt]

#3 randomized controlled trials as Topic[mh]

#4 double-blind method[mh]

#5 single-blind method[mh]

#6 clinical trials as topic[mh]

#7 placebos[mh]

#8 random*[tiab]

#9 (singl* or doubl* or trebl* or tripl*) and (blind* or mask*)

#10 clinical trial*[tiab]

#11 placebo*[tiab]

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 models, animal[mh]

#14 animals[mh]

#15 animal experimentation[mh]

#16 disease models, animal[mh]

#17 animals, laboratory[mh]

#18 humans[mh]

#19 infant, newborn[mh]

#20 (newborn infant*) or newborn* or neonate*[tiab]

#21 #13 or #14 or #15 or #16 or #17

#22 #19 or #20

#23 #21 not #18

#24 #12 not #23

#25 #24 not #22

#26 head or crania* or craniocerebral or capitis or craniu* or cerebra* or cerebru* or brain* or forebrain* or skull* or hemispher* or intracran* or encephal*[tiab]

#27 (oxygen saturation*) or oximetr* or oxygenati* or ScO2[tiab]

#28 oximetry[mh]

#29 #27 or #28

#30 #26 and #29

#31 (near-infrared spectromet*) or (near-infrared spectroscop*) or (spectroscop*, near-infrared) or (NIR spectroscop*) or (spectroscop*, NIR) or (spectromet*, near-infrared)

#32 spectroscopy, near-infrared[mh]

#33 #30 or #31 or #32

#34 operati* or perioperat* or peroperat* or preoperati* or postoperat* or intraoperat* or surg* or (anesthe* recovery)

#35 perioperative care[mh]

#36 perioperative nursing[mh]

#37 specialties, surgical[mh]

#38 #34 or #35 or #36 or #37

#39 #25 and #33 and #38

Appendix 4. Data collection form

CARG

Data collection form

Intervention review—RCTs only

Review title or ID
Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of oxygenation in children and adults

Study ID ***(surname of first author and year first full report of study was published e.g. Smith 2001)***

Report IDs of other reports of this study ***(e.g. duplicate publications, follow-up studies)***

Notes:

1. General information

Date form completed *(dd/mm/yyyy)*

Name/ID of person extracting data

Report title

(title of paper/abstract/report from which data are extracted)

Report ID

(ID for this paper/abstract/report)

Reference details

Report author contact details

Publication type

(e.g. full report, abstract, letter)

Study funding sources

(including role of funders)

Possible conflicts of interest

(for study authors)

Notes:

2. Study eligibility

Study characteristics	**Eligibility criteria** *(Insert eligibility criteria for each characteristic as defined in the Protocol)*	Yes/ No/ Unclear	**Location in text**
Type of study	Randomized controlled trial		

(Continued)

	Controlled clinical trial *(quasi-randomized trial)*
Type of study participants	Relevant participants Adult participants: aged 18 years or older Paediatric participants: younger than 18 years of age, excluding neonates Perioperative period
Types of interventions	Relevant interventions Cerebral NIRS monitoring and intervention correcting CDEs in the perioperative setting Control group: conventional monitors (e.g. heart rate, mean arterial pressure) or other kinds of monitors such as EEG, TCD, BIS, jugular bulb oximetry, evoked potentials, cerebral tissue oxygen partial pressures (PbO_2), etc., either not monitored by cerebral NIRS or monitored but with the $rScO_2$ readout concealed to anaesthesiologists
Types of outcome measures	Relevant outcomes Postoperative neurological injury, postoperative delirium or cognitive dysfunction, mortality The occurrence of abnormal $rScO_2$ during or after surgery; any major non-neurological complications that occur during the intraoperative or postoperative period; hospital length of stay or intensive care length of stay; cost of hospitalization
Reason for exclusion	**INCLUDE** □ **EXCLUDE** □
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description *Include comparative information for each group (i.e. intervention and control) if available*	**Location in text**
Population description *(from which study participants are drawn)*		
Setting		

(Continued)

(including location and social context)
Inclusion criteria
Exclusion criteria
Method/s of recruitment of participants
Informed consent obtained Yes No Unclear
Notes:

4. Methods

	Descriptions as stated in report/paper	**Location in text**
Aim of study		
Design *(e.g. parallel, cross-over, cluster)*		
Unit of allocation *(by individuals, cluster/groups or body parts)*		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study Yes No Unclear		
Notes:		

5.Risk of bias assessment

See Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Domain	Risk of bias			Support for judgement	Location in text
	Low risk	High risk	Unclear		
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					
Blinding of participants *(performance bias)*				**Outcome group: all/**	
(if required)				**Outcome group:**	
Blinding of outcome assessment *(detection bias)*				**Outcome group: all/**	
(if required)				**Outcome group:**	
Incomplete outcome data *(attrition bias)*					
Selective outcome reporting? *(reporting bias)*					
Other bias					
Notes:					

6.Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text
Total no. randomly assigned *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
American Society of Anesthesiologists (ASA) grade		
Comorbidities		
Treatment received for comorbidities		
Surgery type		
Length of surgery		
Subgroups measured		
Subgroups reported		
Notes:		

7.Intervention groups

Copy and paste table for each intervention and comparison group

Intervention group (NIRS group)

	Description as stated in report/paper	Location in text
Group name		
No. randomly assigned to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of NIRS monitoring		
Timing of NIRS monitoring *(in OR, PACU or ICU)*		
Baseline of cerebral oxygenation		
Episode and duration of decline in $rScO_2$		
Treatment of decline in $rScO_2$		
Delivery of anaesthetic agents *(whether TIVA, inhalational agents or both)*		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Notes:		

Control group 1 (No cerebral oxygenation monitoring group)

	Description as stated in report/paper	Location in text
Group name		
No. randomly assigned to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Delivery of anaesthetic agents *(whether TIVA, inhalational agents or both)*		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		

(Continued)

Notes:

Control group 2 (Non-NIRS cerebral monitoring group)

	Description as stated in report/paper	Location in text
Group name		
No. randomly assigned to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of cerebral monitoring		
Timing of cerebral monitoring *(in OR, PACU or ICU)*		
Baseline of cerebral oxygenation		
Episode and duration of decline in cerebral oxygenation		
Treatment of decline in cerebral oxygenation		
Delivery of anaesthetic agents *(whether TIVA, inhalational agents or both)*		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Notes:		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text
Outcome name: postoperative stroke or other neurological injury, including adverse neurodevelopmental outcomes		
Time points measured: within 24 hours postoperatively up to discharge or the end of follow-up		

(Continued)

Time points reported	
Outcome definition **YES/NO**	
Person measuring/reporting	
Unit of measurement *(if relevant)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Power	
Notes:	

Outcome 2

	Description as stated in report/paper	**Location in text**
Outcome name: POD or POCD		
Time points measured: within 24 hours postoperatively up to discharge		
Time points reported		
Outcome definition **YES/NO**		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

Outcome 3

	Description as stated in report/paper	Location in text
Outcome name: intraoperative or postoperative mortality		
Time points measured: during surgery or at 24 hours, 30 days and one year after surgery		
Time points reported		
Outcome definition **YES/NO**		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

Outcome 4

	Description as stated in report/paper	Location in text
Outcome name: occurrence of abnormal $rScO_2$ during or after surgery		
Time points measured: during surgery or within 72 hours after surgery		
Time points reported		
Outcome definition **YES/NO**		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	

(Continued)

Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Power	
Notes:	

Outcome 5

	Description as stated in report/paper	Location in text
Outcome name: any major non-neurological complications that occur during intraoperative or postoperative period		
Time points measured: during surgery or within 24 hours post-operatively up to discharge		
Time points reported		
Outcome definition **YES/NO**		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

Outcome 6

	Description as stated in report/paper	Location in text
Outcome name: length of ICU or hospital stay (in days)		
Time points measured: at discharge from ICU or hospital		
Time points reported		
Outcome definition		

(Continued)

YES/NO	
Person measuring/reporting	
Unit of measurement *(if relevant)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Power	
Notes:	

Outcome 7

	Description as stated in report/paper	Location in text
Outcome name: cost of hospitalization		
Time points measured: at discharge from hospital		
Time points reported:		
Outcome definition: mean difference in cost of hospitalization in US dollar/UK sterling between NIRS group and control group		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper				Location in text
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

10. Applicability

Have important populations been excluded from the study?	Yes No Unclear

(Continued)

(consider disadvantaged populations and possible differences in the intervention effect)		
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	Yes No Unclear	
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	Yes No Unclear	
Notes:		

11. Other information

	Description as stated in report/paper	**Location in text**
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

CONTRIBUTIONS OF AUTHORS

Yun Yu (YY), Kaiying Zhang (KZ), Ling Zhang (LZ), Ruquan Han (RH), Huantao Zong (HZ), Lingzhong Meng (LM)

Conceiving of the review: YY, RH

Co-ordinating the review: YY, KZ, LZ, RH

Undertaking manual searches: HZ

Screening search results: YY, KZ

Organizing retrieval of papers: YY, KZ, RH

Screening retrieved papers against inclusion criteria: YY, KZ

Appraising quality of papers: YY, KZ, LZ, LM

Abstracting data from papers: YY, KZ

Writing to authors of papers to request additional information: YY

Providing additional data about papers: YY, KZ, HZ

Obtaining and screening data on unpublished studies: YY, KZ, HZ

Providing data management for the review: YY, KZ, LZ

Entering data into Review Manager (RevMan 5.3): YY, KZ

Handling RevMan statistical data: YY, KZ

Performing other statistical analysis not using RevMan: KZ, LZ

Interpreting data: YY, KZ, LZ, RH, LM

Making statistical inferences: LZ

Writing the review: YY, KZ, LZ, RH, LM

Securing funding for the review: N/A

Performing previous work that was the foundation of the present study: YY, KZ

Serving as guarantor for the review (one author): RH

Taking responsibility for reading and checking the review before submission: YY, LM

DECLARATIONS OF INTEREST

Yun Yu: none known.

Kaiying Zhang: none known.

Ling Zhang: none known.

Ruquan Han: none known.

Huantao Zong: none known.

Lingzhong Meng: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol (Yu 2014).

1. In this review, we have specified 20% attrition as a criterion to make judgements about incomplete outcome data, which was not specified in the protocol.
2. We analysed data with a random-effects model because we expected clinical and methodological heterogeneity between studies. Therefore, we deleted the planned sensitivity analysis using a random-effects model and a fixed-effect model separately for each outcome variable.
3. We performed subgroup analyses only for the primary outcomes, which was not specified in the protocol.
4. We did not find any quasi-RCTs, therefore we did not conduct a sensitivity analysis based on these studies.
5. We did not perform survival analysis at 24 hours, 30 days and one year because there were no time-to-event data.
6. We did not find any cluster-randomized controlled trials (cluster-RCTs).
7. We did not create a funnel plot to qualitatively assess publication or reporting bias because fewer than 10 studies were included for each outcome.
8. We did not perform subgroup analysis according to age of participants because none of the included studies considered a paediatric population.

9. We generated a 'Summary of findings' table for the comparison 'Active cerebral oxygenation monitoring versus blinded cerebral oxygenation monitoring'. We also included adverse events in the 'Summary of findings' table (and adverse events as a secondary outcome in the review).

INDEX TERMS

Medical Subject Headings (MeSH)

*Spectroscopy, Near-Infrared; Abdomen [surgery]; Arthroplasty, Replacement, Hip; Arthroplasty, Replacement, Knee; Brain [*metabolism]; Cognition Disorders [prevention & control]; Hypoxia-Ischemia, Brain [*diagnosis]; Lumbar Vertebrae [surgery]; Monitoring, Intraoperative; Oxygen Consumption [*physiology]; Postoperative Complications [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans