Physician anaesthetists versus non-physician providers of anaesthesia for surgical patients (Review)

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[Intervention Review]

Physician anaesthetists versus non-physician providers of anaesthesia for surgical patients

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ABSTRACT

Background

With increasing demand for surgery, pressure on healthcare providers to reduce costs, and a predicted shortfall in the number of medically qualified anaesthetists it is important to consider whether non-physician anaesthetists (NPAs), who do not have a medical qualification, are able to provide equivalent anaesthetic services to medically qualified anaesthesia providers.

Objectives

To assess the safety and effectiveness of different anaesthetic providers for patients undergoing surgical procedures under general, regional or epidural anaesthesia. We planned to consider results from studies across countries worldwide (including developed and developing countries).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL on 13 February 2014. Our search terms were relevant to the review question and not limited by study design or outcomes. We also carried out searches of clinical trials registers, forward and backward citation tracking and grey literature searching.

Selection criteria

We considered all randomized controlled trials (RCTs), non-randomized studies (NRS), non-randomized cluster trials and observational study designs which had a comparison group. We included studies which compared an anaesthetic administered by a NPA working independently with an anaesthetic administered by either a physician anaesthetist working independently or by a NPA working in a team supervised or directed by a physician anaesthetist.

Data collection and analysis

Three review authors independently assessed trial quality and extracted data, contacting study authors for additional information where required. In addition to the standard methodological procedures, we based our risk of bias assessment for NRS on the specific NRS risk of bias tool presented at the UK Cochrane Contributors' Meeting in March 2012. We considered case-mix and type of surgical procedure, patient co-morbidity, type of anaesthetic given, and hospital characteristics as possible confounders in the studies, and judged how well the authors had adjusted for these confounders.

Main results

We included six NRS with 1,563,820 participants. Five were large retrospective cohort studies using routinely collected hospital or administrative data from the United States (US). The sixth was a smaller cohort study based on emergency medical care in Haiti. Two were restricted to obstetric patients whilst the others included a range of surgical procedures. It was not possible to combine data as there was a degree of heterogeneity between the included studies.

Two studies failed to find a difference in the risk of death in women undergoing caesarean section when given anaesthesia by NPAs compared with physician anaesthetists, both working independently. One study reported there was no difference in mortality between independently working provider groups. One compared mortality risks between US states that had, or had not, 'opted-out' of federal insurance requirements for physician anaesthetists to supervise or direct NPAs. This study reported a lower mortality risk for NPAs working independently compared with physician anaesthetists working independently in both 'opt-out' and 'non-opt out' states.

One study reported a lower mortality risk for NPAs working independently compared with supervised or directed NPAs. One reported a higher mortality risk for NPAs working independently than in a supervised or directed NPA group but no statistical testing was presented. One reported a lower mortality risk in the NPA group working independently compared with the supervised or directed NPA group in both 'opt-out' and 'non-opt out' states before the 'opt-out' rule was introduced, but a higher mortality risk in 'opt-out' states after the 'opt-out' rule was introduced. One reported only one death and was unable to detect a risk in mortality. One reported that the risk of mortality and failure to rescue was higher for NPAs who were categorized as undirected than for directed NPAs.

Three studies reported the risk of anaesthesia-related complications for NPAs working independently compared to physician anaesthetists working independently. Two failed to find a difference in the risk of complications in women undergoing caesarean section. One failed to find a difference in risk of complications between groups in 'non-opt out' states. This study reported a lower risk of complications for NPAs working independently than for physician anaesthetists working independently in 'opt-out' states before the 'opt-out' rule was introduced, but a higher risk after, although these differences were not tested statistically.

Two studies reported that the risk of complications was generally lower for NPAs working independently than in the NPA supervised or team group but no statistical testing was reported. One reported no evidence of increased risk of postoperative complications in an undirected NPA group versus a directed NPA group.

The risk of bias and assessment of confounders was particularly important for this review. We were concerned about the use of routine data for research and the likely accuracy of such databases to determine the intervention and control groups, thus judging four studies at medium risk of inaccuracy, one at low and one, for which there was insufficient detail, at an unclear risk. Whilst we expected that mortality would have been accurately reported in record systems, we thought reporting may not be as accurate for complications, which relied on the use of codes. Studies were therefore judged as at high risk or an unclear risk of bias for the reporting of complications data. Four of the six studies received funding, which could have influenced the reporting and interpretation of study results. Studies considered confounders of case-mix, co-morbidity and hospital characteristics with varying degrees of detail and again we were concerned about the accuracy of the coding of data in records and the variables considered during assessment. Five of the studies used multivariate logistic regression models to account for these confounders. We judged three as being at low risk, one at medium risk and one at high risk of incomplete adjustment in analysis.

Authors' conclusions

No definitive statement can be made about the possible superiority of one type of anaesthesia care over another. The complexity of perioperative care, the low intrinsic rate of complications relating directly to anaesthesia, and the potential confounding effects within the studies reviewed, all of which were non-randomized, make it impossible to provide a definitive answer to the review question.

PLAIN LANGUAGE SUMMARY

Physician anaesthetists versus nurse anaesthetists for surgical patients

Background

There is an increasing demand for surgery, pressure on healthcare providers to reduce costs, and a predicted shortfall in the number of medically qualified anaesthetists. This review aimed to consider whether anaesthesia can be provided equally effectively and safely by nurse anaesthetists (without medical qualifications) as by medically qualified anaesthetists with specialist training.

Study characteristics

The evidence was current up to 13 February 2013. We found six relevant studies, five of which were large observational studies from the US with a comparison group and with study durations from two to 11 years, and one was a much smaller 12 week study from Haiti. There were over 1.5 million participants in the studies. Information for these studies was taken from American insurance databases (Medicare) and from hospital records. The small study was based on emergency medical care after the 2008 hurricanes in Haiti.

Key results

Most studies stated that there was no difference in the number of people who died when given anaesthetic by either a nurse anaesthetist or a medically qualified anaesthetist. One study stated that there was a lower rate of death for nurse anaesthetists compared to medically qualified anaesthetists. One study stated that the risk of death was lower for nurse anaesthetists compared to those being supervised by an anaesthetist or working within an anaesthetic team, whilst another stated the risk of death was higher compared to a supervised or team approach. Other studies gave varied results. Similarly, there were variations between studies for the rates of complications for patients depending on their anaesthetic provider.

Quality of the evidence

Much of the data came from large databases, which may have contained inaccuracies in reporting. There may also be important differences between patients that might account for variation in study results, for example, whether patients who were more ill were treated by a medically qualified anaesthetist, or whether nurse anaesthetists worked in hospitals that had fewer resources. Several of the studies had allowed for these potential differences in their analysis, however it was unclear to us whether this had been done sufficiently well to allow us to be confident about the results. There was also potential confounding from the funding sources for some of these studies.

Conclusion

As none of the data were of sufficiently high quality and the studies presented inconsistent findings, we concluded that it was not possible to say whether there were any differences in care between medically qualified anaesthetists and nurse anaesthetists from the available evidence.

BACKGROUND

Internationally there are challenges for the provision of anaesthetic services. Current and predicted shortfalls can be explained by an ageing population, increasing demand for surgery, changes to working hours, migration of anaesthetists, pressure on healthcare costs and in some countries a reduction in the number of medical graduates choosing to specialize in anaesthesia (Egger 2006; Egger 2007; Jordan 2011).

Similar pressures are seen in other fields of health care, resulting in a trend towards the use of a nurse-led rather than a traditional doctor-led service, such as in primary care and monitoring of long term conditions. However, the development of similar substitutions within the field of anaesthesia has been met with more resistance (Smith 2005).

With regard to cost containment, there is a substantial difference in the salaries of the two personnel within countries (in the United States (US), for example, the salary of an anaesthetist is approximately double that of non-physician personnel (Kalist 2011)).

Role of non-physician anaesthetists

For the purpose of this review, and to avoid confusion, the word 'physician anaesthetist' is used for all personnel who are medically qualified, and 'non-physician anaesthetist' (NPA) for all those who provide anaesthesia without a medical qualification. This includes a change of terms for discussion regarding some countries, for example, in the US they are normally referred to as 'anesthesiologists' and 'certified registered nurse anesthetists' (or CRNAs), respectively.

There are considerable differences in the organization of anaesthetic teams across Europe and internationally (Egger 2007; Meeusen 2010), where anaesthetics may be administered by physician anaesthetists working alone or as part of an anaesthetic team, or by NPAs who in turn may be working alone or as part of an anaesthetic team (Bacon 2002). Between countries there are also significant differences in the length of training of personnel (Egger 2007; Matsusaki 2011; Meeusen 2010).

Non-physician anaesthetists (NPAs) in developing countries

Low and middle income countries, with large populations living in rural locations, have few physician anaesthetists with ratios of less than one per 100,000 population. For example, Uganda has approximately one physician anaesthetist per two million population (Dubowitz 2010) as opposed to the UK which has 12,000 per 64 million, that is 1:5000 (Walker 2007). These countries have been using non-physician personnel to deliver many anaesthetic services, for example, Kenya's nurse anaesthesia training programme (Newton 2010).

Non-physician anaesthetists (NPAs) in the US

The US has a long history of using nurses to administer anaesthetics. However, as anaesthesia has developed as a physician specialty there is now a majority of medically qualified anaesthetists and considerable debate exists between the two professional groups regarding roles and responsibilities (Bacon 2002; Gardner 2011; Matsusaki 2011). Kalist 2011 says "there is so much overlap between the work they do that it is not clear whether an MDA (physician anaesthetist) actually does anything that a CRNA (NPA) does not do". In recent years, changes to state law in the US with regard to Medicare and Medicaid reimbursement allow some NPAs to now practice without supervision from a physician anaesthetist. At present there are 17 states who have 'opted out' and NPAs can practice as such (AANA Fact Sheet). Millions of dollars have been spent lobbying for or against this ruling (Bacon 2002).

Non-physician anaesthetists (NPAs) in the UK and other developed countries

In other developed countries there is variation in the changing roles and responsibilities of anaesthetic providers. A move in some European countries now sees NPAs able to induce general anaesthesia for American Society of Anesthesiologists (ASA) I and II patients under the indirect supervision of a physician anaesthetist (for example, in Denmark, France, Norway and Sweden), whilst in some countries (for example, Netherlands and Norway) nurse anaesthetists with additional training are also able to give sedation under monitored anaesthesia care (MAC), again under indirect supervision (Meeusen 2010). These countries however continue to resist a move towards unsupervised NPAs. In the UK, the introduction of an anaesthesia physician assistant, now called physician assistant (anaesthesia) (PA(A)), pilot training programme from October 2003 attempted to address the predicted shortfall of physician anaesthetists (Wilkinson 2007). However, there are limits to the responsibilities given to a PA(A) and they are provided with supervision from a physician anaesthetist. After the introduction of PA(A)s, the Association of Anaesthetists of Great Britain and Ireland maintains an opinion that "the highest standards of anaesthesia can only be achieved by a physician-only service" (AAGBI 2010).

Despite differences in opinion regarding the length of training of NPAs in some countries, the potential benefits of independent practice are evident, particularly in rural areas which attract fewer anaesthetists.

Impact of use of non-physician anaesthetists (NPAs) on patient care

The debate over the use of NPAs has focused on patient safety and the question of whether different providers deliver equivalent quality and safety to patients.

A systematic review has been carried out by Smith et al (Smith 2004). They identified four articles relevant to the review question, none of which were randomized controlled trials (RCTs). The authors were unable to show any significant difference in the safety of using different anaesthetic providers, however they also concluded that, given the methodological flaws in the available studies, this was not evidence of absence of a difference.

Apart from anxieties over patient safety, there are other factors involved in how far the role of an NPA should be developed, such as threats to medically qualified physician anaesthetists' professional status, access to training and working practices, as well as the wish to avoid the costly and lengthy interprofessional conflict that exists in the US (Kane 2004; Smith 2005).

Why it is important to do this review

Increasing demands on healthcare systems together with a predicted personnel shortfall and the current emphasis on cost containment make this a timely and important review.

This review updates Smith's existing review (Smith 2004) and aimed to establish what is known about patient safety when anaesthetics are administered by different personnel. We hoped that this may lead to an increase in confidence in the skills of NPAs within the anaesthetic community and may potentially lead to greater flexibility in team roles, both within and between countries, depending on patient need.

OBJECTIVES

To assess the safety and effectiveness of different anaesthetic providers for patients undergoing surgical procedures under general, regional or epidural anaesthetic.

A subsidiary question was to determine whether there are types of procedures or patient groups for which a non-physician anaesthetist is not appropriate. We planned to consider results from

studies within different regions (US, UK, other developed countries and developing countries) initially and then assess whether the results were consistent across regions before combining results.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include RCTs, quasi-randomized trials in which the allocation to the intervention was decided by non-random means (such as alternation, digits in date of birth or other identification (ID) number) and cluster randomized trials.

In the absence of RCTs, we included non-randomized controlled trials (NRCTs) and non-randomized cluster trials. We considered all designs of observational studies which included a comparison group, including prospective and retrospective cohort study designs, controlled before-after study designs, prospective and retrospective case-control study designs and interrupted time-series. We did not include descriptive studies without a direct comparison group.

If we had identified any RCTs we planned to consider non-randomized studies (NRS) separately and not include them in a meta-analysis.

Types of participants

We included studies of patients of all ages undergoing emergency or elective surgery under general or regional anaesthetic in a hospital setting. We also included patients undergoing obstetric surgery.

Types of interventions

We included studies which compared an anaesthetic administered by an NPA working independently with either:

1. an anaesthetic administered by a physician anaesthetist working independently;
2. an anaesthetic administered by a NPA working in a team which was supervised or directed by a physician anaesthetist.

We have taken into consideration the difference in terminology of anaesthetic personnel between countries, which can potentially lead to confusion (Vickers 2002). Throughout we have used the terms 'physician anaesthetist' and 'non-physician anaesthetist' (NPA), as defined above. Examples of different names for anaesthetic personnel are given in Appendix 1. Where a study author used an unclear term to describe an anaesthetic provider that we were unable to designate to one of the above categories, we aimed to contact the authors to seek clarification. There are also various terms used to describe the role of the main anaesthetic practitioner within a team. Some NPAs may be described as being 'medically directed' (anaesthetic is performed by an NPA whilst the physician anaesthetist oversees no more than four concurrent procedures) or working 'under supervision' (anaesthetic is performed by an NPA who is directed by a physician other than the physician anaesthetist). We ensured that we followed the above definitions as far as possible, aiming to contact authors for clarification if necessary to avoid misclassification of the intervention and comparison in the studies.

Types of outcome measures

Primary outcomes

1. Mortality within 30 days of anaesthetic
2. Failure to rescue between induction and full recovery ("defined as the rate of death after complications" (Silber 2000a))
3. Anaesthesia-related complications (including cardiac, pulmonary and central nervous system complications due to anaesthesia all within 30 days of anaesthetic)

Secondary outcomes

1. Other minor anaesthetic complications (such as nausea and vomiting, pain, sore throat, dental damage) within 48 hours
2. Length of hospital stay
3. Cost
4. Patient reported satisfaction

Search methods for identification of studies

Electronic searches

We searched for eligible trials in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 2), MEDLINE (via Ovid) (from 1985 to February 2014), EMBASE (via Ovid) (from 1985 to February 2014) and CINAHL (via EBSCO) (from 1985 to February 2014). We also searched trial registers, www.clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (http://www.who.int/ictrp/network/en/), for ongoing trials. We also searched Health Management Information Consortium (HMIC) via Ovid, which includes grey literature.

The search strategies for MEDLINE, EMBASE, CINAHL and CENTRAL are presented in Appendix 2. The search strategy did not include any outcomes and was not limited by study design or publication type. No language restrictions were imposed. On retrieval of studies we assessed any free text terms or MeSH terms

for NPAs, and if we had not used them we would have included these in a modified search strategy.

Searching other resources

We identified other relevant systematic reviews in the search and undertook forward and backward citation tracking for key articles. We contacted study authors to ask if they knew of other relevant ongoing or unpublished studies. In September 2013 we searched the following clinical trials databases: ClinicalTrials.gov, the metaRegister for Controlled Trials, and the WHO International Clinical Trials Registry Platform.

Data collection and analysis

Selection of studies

Results of the searches were collated and duplicates removed. All titles and abstracts were screened by two authors (Sharon R Lewis (SRL) and Amanda Nicholson (AN)) to remove studies that were very unlikely to be eligible. A pilot of 100 titles was performed before all titles were reviewed in order to clarify criteria for discarding articles at this stage. We planned to identify potentially eligible RCTs and NRS separately. If no abstract was available but the title was possibly relevant, the full text of the article was obtained. We anticipated that we would need to get more full texts for observational studies as abstracts may not contain sufficient detail to allow classification (Section 13.3.1.3) (Higgins 2011).
When all titles and abstracts were screened, the full texts of potentially relevant titles were reviewed by SRL and AN and the data were recorded on the study eligibility section of the data extraction form. We planned to have separate eligibility forms for RCTs and NRS (copies are included in Appendix 3). The NRS eligibility form used study design features rather than study design labels, based on the tools presented at the UK Contributors' Meeting 2012, which were then modified to suit our review needs. These features fall into four groups: Was there a relevant comparison? How were the groups formed? Were the features of the study described below carried out after the study was designed? On what variables was comparability of groups assessed? These were incorporated into the data extraction form (Appendix 3).
A pilot selection of 10 papers were read by SRL and AN and then the investigators met to compare results and modify the forms as required. SRL and AN then read all potentially relevant papers and met to compare results. We referred any differences that could not be resolved by discussion onto Andrew F Smith (AFS).

Data extraction and management

Data were extracted from eligible studies by SRL, AN and Phil Alderson (PA) using a paper-based data extraction form (see Appendix 3). This form was reviewed after data from the first three papers had been entered, and modified as required. If duplicate publications from the same study were identified, we created a composite dataset from all the eligible publications.
The following items were included in the NRS data extraction form:

- methods, to include risk of bias assessments (see below);
- patient group, to include age, sex, relevant sociodemographics, case-mix;
- setting, e.g. rural or urban, country;
- intervention, to include training, experience and the level of supervision, role and responsibilities of NPA;
- comparison, to include training and experience of anaesthetist;
- outcome, to include time points i. measured and ii. reported, unit of measurement;
- analytic methods including Unit of analysis issues;
- results, to include missing participants, subgroup analyses, both unadjusted and adjusted results.

If relevant information or data were not available in the paper, we attempted to contact the lead author to request the additional details. Disagreements were resolved by discussion and, if necessary, consultation with AFS.

Assessment of risk of bias in included studies

We anticipated that we would encounter a range of NRS designs. We based our risk of bias assessment for NRS on the specific NRS risk of bias tool presented at the UK Contributors' Meeting 2012 (incorporated into the data extraction form for NRS (Appendix 3)).
The direction and impact of bias across different NRS is dependent on individual study features and hence hugely variable and difficult to predict (Deeks 2003). In this review, selection bias and confounding by indication were of particular concern.
Risk of bias for each domain was judged as high, low or unclear, unless specified otherwise.

Allocation (selection bias).

As part of our assessment of study design we recorded the factors which determined participant allocation to the intervention or control group.

Blinding (performance and detection bias)

Accuracy with which the intervention or control group determined

We recorded whether the study personnel or participants were blinded to the allocation of participants and any other measures

taken to ensure that the treatment of intervention and comparison groups were equivalent in all aspects other than anaesthetic provider. In addition we recorded the methods and data used to decide which patients belonged to the intervention or comparison group, with an estimate of the risk of inaccuracy scored as high, medium, low or unclear.

Accuracy with which outcomes assessed

For studies using routine hospital data there may be errors or omissions in recording outcomes, depending on coding practice within the hospital. Failure to rescue rates, which rely on the recording of a complication before death, have been shown to be very sensitive to the completeness of coding of these secondary diagnoses (McKee 1999). If the intervention and comparison groups were in different hospitals with different coding practices this may have a considerable influence on results. We assessed whether the outcome data were recorded with knowledge of the anaesthetic provider group (blinding) and also assessed the risk of inaccuracy of outcome data, scored as high, medium, low or unclear.

Incomplete outcome data (attrition bias)

This largely depends on the accuracy and completeness of outcome data. This relies in part on the accuracy with which outcomes are identified within the dataset, as discussed above, but also on the coverage of the outcome dataset. Important questions include whether all participants were correctly identified and linked to the outcome dataset.

Selective reporting

Registration of protocols and analysis plans is not as common for observational studies as for RCTs and there is scope for the study authors to present results only on outcomes found to be significantly associated with the intervention of interest. This is a particular risk when routine data are used which have considerable scope to study a range of different outcomes. We recorded whether the study authors had published analysis plans or protocols.

Other potential sources of bias

We considered the funding sources for each study and any resulting potential conflicts of interest.

Assessment of control for confounding factors

Important confounding factors for this research question are:

- case-mix and type of surgical procedure;
- patient co-morbidity;
- type of anaesthetic given;
- hospital characteristics.

All these variables are plausibly associated both with participant outcome and with the type of anaesthetic provider and so could account for any observed association between anaesthetic provider and participant outcome.

Using the data extraction form (Appendix 3) for each NRS we:

- identified the relevant confounders described by the researcher;
- identified the method for identifying relevant confounders as described by the researchers;
- scored all confounders, including those not specified by the researchers for

1. the risk of imprecision in measurement of confounder, scored as high, medium, low or unclear,
2. the risk of imbalance in confounder between provider groups, scored as high, medium, low or unclear;

- identified the method used for controlling for confounding at both the design and analysis stage;
- judged the risk of incomplete adjustment during analysis as high, medium, low or unclear.

Measures of treatment effect

On the data extraction form we recorded all unadjusted and adjusted effect estimates for all eligible outcomes, with details of confounders included for each estimate. Regression coefficients or analysis of covariance would have been recorded for continuous variables.

In an attempt to control for confounding, we used adjusted rather than unadjusted effect estimates from NRS in the analysis and discussion of study findings. If multiple adjusted estimates were given we used the estimate that included the largest number of our pre-determined key confounders.

Unit of analysis issues

The intervention or comparison group may be decided or assigned at a hospital level and this needed to be accounted for in any analysis, since these hospitals may differ in many respects other than anaesthetic provider. Incorrect analysis would result in residual confounding in the model or inaccurate confidence intervals. The use of multi-level or hierarchical models or robust standard errors was recorded and if the appropriate analysis was not reported we planned to contact the authors.

Dealing with missing data

We contacted study authors to request missing outcome data or any other methodological details. Missing outcome data were likely to be more of an issue in RCTs or prospective cohort studies, where data are collected specifically for the study. If we had suitable data, we planned to undertake sensitivity analyses to assess the impact of the missing outcomes using, for example, worst

case scenario, last observation carried forward and available case analysis.

Assessment of heterogeneity

We expected to find more heterogeneity between NRS than between RCTs, reflecting differences in study design and scope for bias, as well as intrinsic differences in the intervention (Sections 13.6.2.3 and 13.6.2.4) (Higgins 2011). It has been estimated that heterogeneity leads to uncertainty 5 to 10 times that of a 95% confidence interval (Deeks 2003). If we had comparable results for outcomes in different studies we planned to use a forest plot to display the most adjusted estimates from each study and to use Chi^2 and I^2 statistics to describe heterogeneity. Study characteristics that may be important include:

- number of confounders included in models;
- analysis technique used;
- type of data collection.

Assessment of reporting biases

Reporting bias and missing studies are a more complex issue for NRS than for RCTs. Registration and publication of protocols for observational studies is not as widespread as for RCTs so it is not easy to identify the finite population of studies to be included. For this research question there is in fact an existential question concerning the definition of an eligible study. Since routine hospital databases are used in many studies, it could be argued that the pool of eligible studies would include all hospitals which utilize a range of anaesthetic providers and have electronic longitudinal health databases. It clearly would not be possible to access all these databases. It is not clear whether the size of a study or direction of effect are likely to be associated with likelihood of publication, given that many hospital studies are very large but of uncertain quality. These uncertainties undermine the use of a funnel plot.

We aimed to include a wide range of studies using a wide search and did not exclude any potentially eligible articles without reference to the full text.

Data synthesis

We did not pool estimates of effects from NRS studies(Sections 13.6.2.3 and 13.6.2.4) (Higgins 2011).

If we had comparable effect estimates we would have displayed the most adjusted results from each study in a forest plot but without a pooled estimate. As the results from studies were too disparate to display together in a forest plot we have used narrative synthesis to summarize the direction, size and consistency of effects across studies.

RESULTS

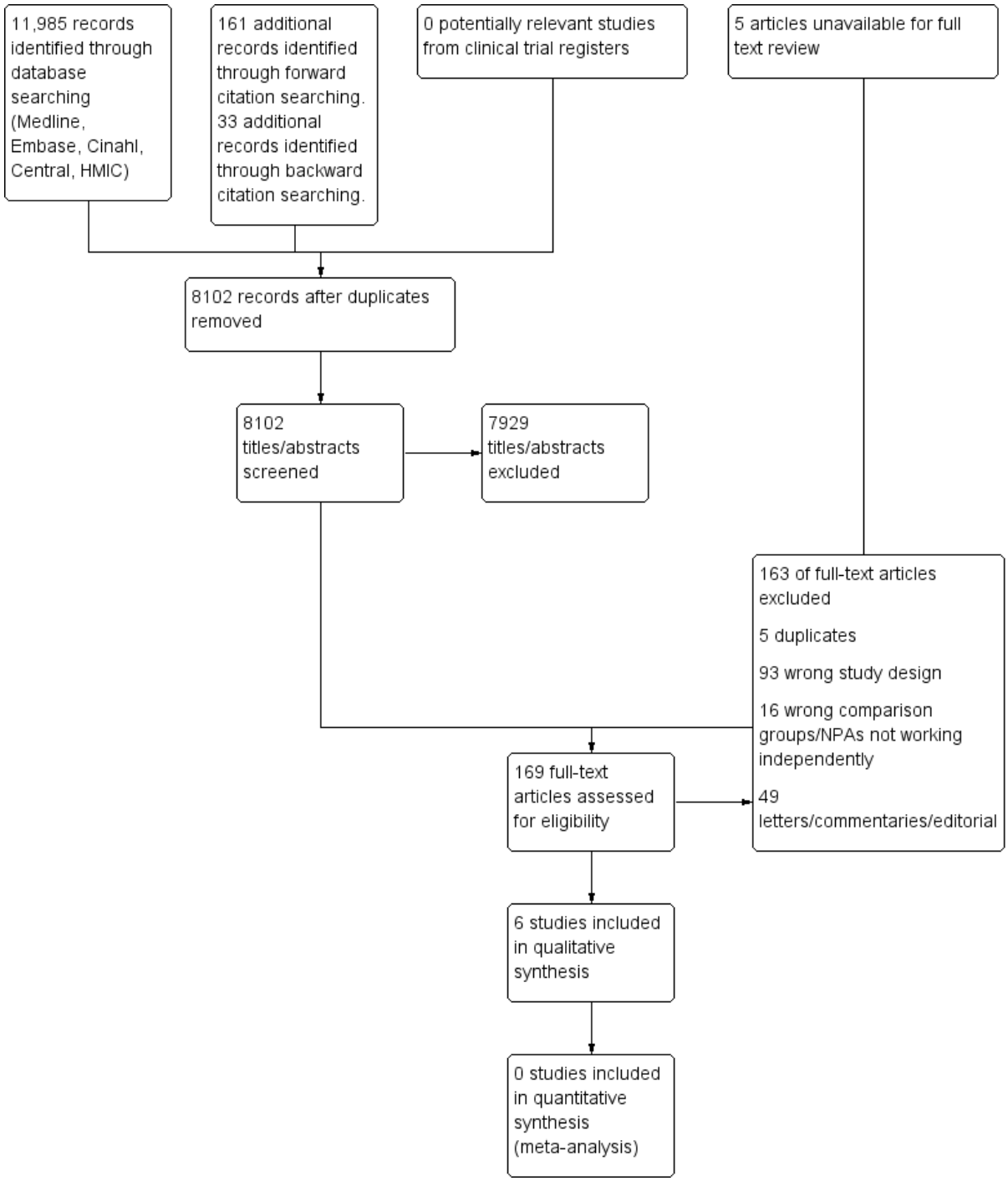
Description of studies

Summary details of each study are in Characteristics of included studies.

Results of the search

There were 11,985 studies identified from electronic searches, 161 studies from forward citation searching and a further 33 from backward citation searching. No studies were identified from clinical trial databases. Having removed duplicates, a total of 8102 unique titles and abstracts were considered and then a further 169 full texts assessed for eligibility. We were unable to obtain full texts for five studies and these are listed in Studies awaiting classification. We performed data extraction and risk of bias assessment on six studies. For the search flow diagram, see Figure 1.

Figure 1. Study flow diagram.



Included studies

Study design

We found no eligible RCTs. All six studies included in the review were non-randomized. Five studies were retrospective cohort studies using routinely collected hospital or administrative data from participants in the USA (Dulisse 2010; Needleman 2009; Pine 2003; Silber 2000a; Simonson 2007). One of these US studies also included a controlled before and after component presenting results in certain states before and after they opted out from the requirement that NPA be supervised (Dulisse 2010). These studies were large, all with more than 100,000 participants, and the total number of participants across all five studies was over 1.5 million. The sixth study was a smaller cohort study, with 330 participants, based in emergency medical care after the 2008 hurricanes in Haiti (Rosseel 2010).

Study population

Two studies were restricted to obstetric patients (Needleman 2009; Simonson 2007) but the other studies included a range of surgical procedures (Dulisse 2010; Pine 2003; Silber 2000a) and Rosseel 2010 focused on emergency surgery only. Three studies used US Medicare data to determine anaesthetic provider and so the study population was aged over 65 years (Dulisse 2010; Pine 2003; Silber 2000a). Pine 2003 studied elective cases for selected operations (carotid endarterectomy, cholecystectomy, herniorrhaphy, hysterectomy, knee replacement, laminectomy, mastectomy or prostatectomy). These were selected so that the study population would be homogenous. Dulisse 2010 excluded day surgery cases because of uncertainty in measuring mortality or complications in these patients.

Intervention and comparison groups

Five studies reported data for NPAs working independently (Dulisse 2010; Needleman 2009; Pine 2003; Rosseel 2010; Simonson 2007). Dulisse 2010, Needleman 2009, Simonson 2007 and Pine 2003 reported a comparison group of a physician anaesthetist working independently.

The studies varied in the definition of an NPA working under supervision or in a team. Dulisse 2010 had a comparison group of an NPA working as part of an anaesthetic team and Pine 2003 had a comparison group of the anaesthetic being administered by a 'team' which included a physician anaesthetist and NPA but it was not stated who exactly administered the anaesthetic. Needleman 2009 had three comparison groups of NPAs working in a team or being supervised: ANES - CRNA I if a physician anaesthetist was required at all planned caesarean sections; ANES - CRNA II if the physician anaesthetist was not required at all planned caesarean sections; and MIXED in which the team varied depending on location. In Rosseel 2010 the physician anaesthetist supervised the NPA in the control group. We considered all of these comparisons as a single group of NPA working under supervision or in a team. Silber 2000a had intervention and comparison groups of undirected and directed NPA using Medicare definitions (Medicare Policy 2005). The undirected group included cases where anaesthesia was delivered by the NPA alone or supervised rather than directed by a physician anaesthetist or directed by a non-anaesthetist physician. Unbilled cases were also included in this group. The comparison directed group combined cases in which the physician anaesthetists had personally performed the anaesthetic and cases in which the NPA performed the case under physician anaesthetist direction. We kept this study as a separate comparison group.

Time period of study

The five studies based in the US used data collected prior to 2005 with the earliest study period being 1991 to 1994 (Silber 2000a) and the latest 1995 to 2005 (Dulisse 2010). For Rosseel 2010 the study period was for 12 weeks in the autumn of 2008.

Outcomes reported

All studies reported mortality. Some studies specified inpatient mortality (Dulisse 2010; Pine 2003). In other studies the time period was not specified but as the data were collected from discharge data we assumed it was in-hospital mortality (Needleman 2009; Simonson 2007). Silber 2000a reported mortality within 30 days of admission.

Failure to rescue (defined as 30 day death rate in those in whom either a complication developed or who died without a complication being recorded) was reported separately only by Silber 2000a but was included in the list of anaesthesia-related complications reported by Dulisse 2010.

Four studies reported complications (Dulisse 2010; Needleman 2009; Silber 2000a; Simonson 2007) which were often presented in amalgamated groups and it was therefore not possible to extract data on serious airways complications as we had originally planned. We have used the modified outcome of anaesthesia-related complications. If study authors divided complications into anaesthesia-related complications (such as International Classification of Diseases (ICD) 9 668.0 codes for complications from labour anaes-

thesia in Needleman 2009 and Simonson 2007) or more general complications we used the data on anaesthetic-related complications. The definition of complications used in Simonson 2007 added other ICD codes from the list of patient safety indicators from the Agency of Healthcare Research and Quality (AHRQ). Dulisse 2010 used a list of seven relevant patient safety indicators to define complications, including failure to rescue. Silber 2000a presented data on a single group of postoperative complications which were not all anaesthesia-related.

No studies reported data on any of our secondary outcomes of length of stay, cost or patient satisfaction.

Excluded studies

There were eight studies that were given particular consideration before exclusion, as listed in Characteristics of excluded studies. Four of these studies did not report data for NPAs working independently (Charuluxananan 2008; Hoffmann 2002; Leonard 2012; Maaløe 2000). In two studies it was unclear whether the NPA was working unsupervised. We successfully contacted the authors of these studies, one of whom was able to confirm that they were supervised (Faponle 2004) and the other was unable to confirm due to the length of time since the report was published (Fleming 1992). One study provided no analysis of data by provider type (Charuluxananan 2005) and Abouleish 2004 did not have any surgical patients.

Other reasons for exclusion included that the reports or abstracts had the wrong study design; had the wrong comparison groups; or were letters, commentaries or editorials with no primary data reported.

Studies awaiting assessment

We considered the full texts of two studies for which we were unable to make a decision regarding eligibility without further information. We attempted to make contact with the author of Carpentier 2000 to establish whether the NPA was working unsupervised as well as the author of Gadir 2007 to establish denominator values for all the data presented. We are still awaiting responses. We were unable to access the full texts of five further studies and have attempted contact with the authors to request copies. See Studies awaiting classification.

Risk of bias in included studies

Risk of bias assessments were completed for all studies. It was intended that a number scoring system (1 to 5) be used for judgements but in practice this was completed using judgements of high, medium or low.

Allocation

All studies were non-randomized with the allocation to the intervention group based on location differences or healthcare decision makers or participant preference. All studies were therefore at high risk of allocation and selection bias. There was evidence of differences in case-mix and co-morbidity between the intervention and comparison groups. See the 'Assessment of control for confounding factors' section.

Blinding

Performance bias

In NRS, blinding of participants and personnel to the allocation of participants is often impossible. None of the included studies were blinded and no specific measures were taken to make sure that the care of the intervention and comparison groups were equivalent in all aspects other than anaesthetic provider. These studies are therefore at high risk of performance bias. Differences in the hospital facilities are an important potential source of bias, which is discussed in the section 'Assessment of control for confounding factors'.

Accuracy with which intervention or control group determined

The use of routine data for research purposes raises an issue about the accuracy of the data used. Three studies based in the US used Medicare part B (billing data) to assign participants to the intervention and comparison groups (Dulisse 2010; Pine 2003; Silber 2000a). It can be difficult to be confident about whether, for example, a physician anaesthetist was actually administering the anaesthetic and the studies dealt with this uncertainty in different ways. Dulisse 2010 assigned cases as NPA alone or physician anaesthetist alone if there was a claim for only one anaesthetic provider. Participants were assigned to NPA team anaesthesia if there was a modifier on either the physician anaesthetist or NPA claim indicating supervision or direction of the NPA. In addition, cases with no part B form were assigned to NPA team anaesthesia if the procedure took place in a 'pass-through' hospital. It is unclear how accurate this assumption is or how many cases were involved so we assessed the risk of inaccuracy as medium. Pine 2003 excluded all cases with missing or ambiguous provider codes and we assessed this study as low risk of inaccuracy. Silber 2000a classified the intervention groups as undirected or directed and the undirected group included a large number of unbilled cases but sensitivity analyses with these cases removed gave the same results. Participants with multiple anaesthetics in one single admission were classed as undirected if during any one day of admission there had been no directed anaesthesia procedures. This may have

the effect of assigning complex high risk cases as undirected. We assessed this study as at medium risk of inaccuracy.
In the other two US studies, both looking at obstetric patients (Needleman 2009; Simonson 2007), the intervention or comparison group was assigned at hospital level based on surveys about usual anaesthetic personnel at the hospital. This raises unit of analysis issues if the intervention group has been assigned at the level of a hospital but individual patient outcomes are analysed. We judged both these studies as at a medium risk of inaccuracy.
Rosseel 2010 gave no details of how the data on provider were collected and we assessed this study as at unclear risk of inaccuracy.

Accuracy with which outcomes assessed

Detection bias and the accuracy with which outcomes were determined were judged for each outcome measure.
We assumed that recording of mortality would be complete and unaffected by allocation group. Detection bias was therefore judged to be at low risk of bias for this outcome. All-cause mortality was not reported so it was not possible to identify deaths related to anaesthetic complications.
Complication recording was less clear and usually relied on coding of discharge data. There were several issues that may lead to inaccuracy. Differentiation of complications from existing co-morbid conditions may be difficult. The accuracy with which outcomes were determined in Silber 2000a was assessed as unclear for both failure to rescue and complications as new complications were differentiated from existing co-morbidities only on the basis of timing of the code (co-morbid conditions coded in the three months prior to admission). Dulisse 2010 gave few details of the data source used to assess complications and was assessed as at unclear risk. It was likely that there are differences in coding practices between hospitals, which is a potential source of bias especially in studies in which the anaesthetic provider was assigned at hospital level. We thought that the recording of complications in Needleman 2009 was at high risk of inaccuracy and bias given that anaesthetic provider status was assigned at hospital level and there was the possibility that the coding of discharge data may vary between hospitals.

Incomplete outcome data

The risk of incomplete outcome data in retrospective cohort studies was in part determined by the accuracy of the data used, as discussed above. A further concern was the coverage of the dataset. These studies reported on large numbers of participants and used different sources of data. None of the studies reported details of how records of the same participant from different administrative databases were linked. Few details were given of the number of missing records or failure to link records. Given the high volume of participants, it seemed implausible that a fully coded discharge abstract or data record was identified for each participant. We assessed all the retrospective cohort studies as at unclear risk of attrition bias. With a study population of 330 in one surgical unit, Rosseel 2010 was assessed as at low risk.

Selective reporting

No a priori protocols or analysis plans were available during a search of clinicaltrials.gov for all studies. There was an unclear potential for reporting bias due the number of possible codes which authors could select for outcome data and analysis.

Other potential sources of bias

Both Dulisse 2010 and Needleman 2009 received funding from the American Association of Nurse Anesthetists (AANA) and this was considered a high risk of bias for these studies. Neither Pine 2003 nor Simonson 2007 received funding for their studies and they were therefore considered at low risk of bias. Rosseel 2010 provided an evaluation of a training programme established by Mèdecins Sans Frontières (MSF) and as all the authors worked for MSF it was assumed that it was at high risk of bias. Silber 2000a stated that the study had been largely self-funded but that background methodology work had been supported by grants from AHRQ and The American Board of Anesthesiology (ABA). It was unclear whether the support from the American Board of Anesthesiology could have biased the study.

Assessment of control for confounding factors

The table of confounders (Appendix 4) summarizes our assessment of the measures taken by study authors to control for potential confounding factors.

Case-mix

Two of the included studies were restricted to caesarean sections (Needleman 2009; Simonson 2007) and were assessed as at low risk of imprecision and imbalance. Three other studies (Dulisse 2010; Pine 2003; Silber 2000a) included adjustment for differences in case-mix in the statistical models. These data were based on Medicare databases and were assessed as at low risk of imprecision. There were often large differences in case-mix between the physician anaesthetist and NPA cases with more complex cases such as cardiovascular surgery more likely to be physician anaesthetist-only or team anaesthesia than NPA-only so we assessed the studies as at high risk of imbalance. Rosseel 2010 reported large differences in case-mix between provider groups but with one death only in the dataset the authors did not adjust the results.

Co-morbidity

Pre-existing conditions which affected the risk of a participant suffering a complication after surgery were considered by five studies (Dulisse 2010; Needleman 2009; Pine 2003; Silber 2000a; Simonson 2007). These data were based on coded data in the discharge summary or in the Medicare or hospital database. None of the studies used other data sources such as free text in hospital notes or independent data collection. The major concern was the completeness of these coded data for underlying conditions or risk factors and the differentiation of existing co-morbidity and new complications. No studies included smoking as a patient characteristic. Dulisse 2010 included only age, sex and race, and no other individual data, and we judged this study to be at high risk of imprecision. Silber 2000a adjusted for 27 coded patient characteristics but only if these codes were used in the three months before admission. We considered that many underlying conditions would not be coded in this way and therefore assessed this study as at high risk of imprecision. Pine 2003 used codes for principal and secondary diagnoses to assess co-morbidity. These authors referred to a more complete database to assess which conditions were most likely to be pre-existing and which were new complications and we assessed this study to be at medium risk of imprecision.

Needleman 2009 and Simonson 2007 used a list of obstetric co-morbidities and both were assessed as at medium risk of imprecision. Needleman 2010 revised their analysis to include more codes for obesity and hypertension following the commentary by Neuman 2010.

Silber 2000a and Simonson 2007 reported important differences in co-morbidity between the intervention and comparison groups with NPA-only cases more likely to be emergency admissions. Dulisse 2010 reported only minor differences in race but used a restricted definition of co-morbidity. Needleman 2009, Pine 2003 and Rosseel 2010 did not report on co-morbidity in the different groups.

Type of anaesthetic given

No studies considered this as a confounder. This meant that different provider groups may have used different types of anaesthesia, for example, a spinal rather than a general anaesthetic for a certain surgical procedure, but this could not be assessed.

Hospital characteristics

Four studies considered this confounder (Needleman 2009; Pine 2003; Silber 2000a; Simonson 2007). The data were based on American Hospital Annual Surveys (AHA) (Needleman 2009; Pine 2003; Silber 2000a) or the study authors' own hospital survey, or both (Needleman 2009; Simonson 2007). None of these survey data were independently verified but the studies differed in the number of characteristics included. Studies using AHA included a range of items assessing location, staffing, teaching status and technological sophistication and we assessed these as at medium risk of imprecision. Simonson used a more limited, variable set including only size, urban or rural location and teaching status and we assessed this study as at high risk of imprecision. All these studies reported important imbalances, with NPA-only cases more likely to be based in rural, smaller hospitals with fewer facilities, and were judged as at high risk of imbalance.

Dulisse 2010 analysed data from many different hospitals across the USA but did not adjust for hospital characteristics.

Rosseel 2010 was based in a single surgical centre.

Analysis method

Multivariate logistic regression models were used in five studies (Dulisse 2010; Needleman 2009; Pine 2003; Silber 2000a; Simonson 2007). Rosseel 2010 reported one death only and did not present adjusted results. Dulisse 2010, Pine 2003 and Silber 2000a gave methods for model building and we assessed these studies to be at low risk of errors due to adjustment in analyses. Pine 2003 presented indirectly standardized mortality rates for the different anaesthetic provider groups. Expected mortality rates were calculated using procedure-specific, stepwise logistic regression models. Needleman 2009 gave no strategy for model building and did not report unadjusted rates or numbers of events or denominators to assess model fit and was assessed as at medium risk of errors due to adjustment in analyses. In Simonson 2007 the rationale for the selection of variables into the final model was not clear. The final model included variables for other labour complications including maternal distress, shock, hypotension and cardiac arrest. We thought that these variables were potentially measures of anaesthetic outcome, or on the causal pathway to anaesthetic complications or mortality, and so they should not have been included in the model. We assessed this study as at high risk of incomplete adjustment in analyses. Simonson 2007 used an appropriate hierarchical model to account for the clustering of intervention data in their analysis and Needleman 2009 adjusted standard errors for clustering within hospitals.

Effects of interventions

Comparison 1: NPA working independently versus physician anaesthetist working independently

Four studies investigated this comparison, two on general surgical patients (Dulisse 2010; Pine 2003) and two on women having caesarean sections (Needleman 2009; Simonson 2007).

Mortality

All four studies reported mortality in the intervention and comparison groups. Needleman 2009 and Simonson 2007 failed to find

a difference in the risk of death in women undergoing caesarean section with anaesthetic given to participants by NPAs working independently compared with those given anaesthetic by physician anaesthetist alone. In Pine 2003 there were no significant differences in mortality between the provider groups in either unadjusted or adjusted analyses. Dulisse 2010 reported adjusted results using anaesthesia by a physician anaesthetist working independently in non-opt out states as the reference group. The risk of mortality was lower in cases given anaesthesia by NPAs working independently in both non-opt out and opt-out states. This difference was statistically significant within non-opt out states but it was not possible to assess the statistical significance between provider groups in opt-out states. This study did not, however, adjust for hospital characteristics. See Analysis 1.1 (Table 1).

Complications

Three studies reported the risk of anaesthesia-related complications (Dulisse 2010; Needleman 2009; Simonson 2007). Needleman 2009 and Simonson 2007 failed to find a difference in the risk of complications in women undergoing caesarean section with anaesthetic given by NPAs working independently compared with those given anaesthesia by physician anaesthetists alone. Dulisse 2010, using the cases given anaesthesia by a physician anaesthetist working independently in non-opt out states as the reference group, failed to find a difference in risk of complications between groups in non-opt out states. In opt-out states the pattern varied with odds ratios lower for NPA alone than physician anaesthetists alone before opt-out but higher after opt-out, but it was not possible to test these differences statistically. See Analysis 1.2 (Table 2).

Comparison 2: NPA working independently versus NPA working in a team which is supervised or directed by a physician anaesthetist

Four studies investigated this comparison, three in general surgical patients (Dulisse 2010; Pine 2003; Rosseel 2010) and one in women having caesarean sections (Needleman 2009). Two studies (Dulisse 2010; Needleman 2009) had several comparison groups and results were presented using the physician anaesthetist working independently as the reference group. This meant that it was not possible to assess the statistical significance of the differences between NPA working independently and NPA working under supervision or in a team, but the relative size of the odds ratios gave an indication of whether mortality or complication risk was higher or lower.

Mortality

In Needleman 2009 the risk of mortality was lower in the NPA-only group than in the NPA supervised or team group. In Dulisse 2010 the pattern varied with the mortality risk lower in the NPA-only group in non-opt out states and opt-out states before opt-out but higher in opt-out states after opt-out. In Pine 2003 the mortality risk was higher in the NPA-only group than in the NPA supervised or team group but no statistical testing of any of these differences was presented. Rosseel 2010 reported one death only in a study of 330 participants and so no difference in mortality risk was detected. See Analysis 2.1 (Table 3).

Complications

Results presented in Dulisse 2010 and Needleman 2009 were similar to those for mortality, with the risk complications generally lower in the NPA-only group than in the NPA supervised or team group, but no statistical testing was reported. See Analysis 2.2 (Table 4).

Comparison 3: undirected NPA versus directed NPA

Silber 2000a presented data for this comparison, in which the intervention undirected group included cases where anaesthesia was delivered by NPA alone, or a NPA was supervised rather than directed by a physician anaesthetist, or a NPA was directed by a non-anaesthetist physician. The comparison-directed group combined cases in which the physician anaesthetists had personally performed the anaesthetic and cases in which the NPA performed the case under physician anaesthetist direction.

There was some evidence that the risk of mortality and failure to rescue was higher in the undirected NPA group, with adjusted odds ratios (OR) of 1.08 (95% confidence interval (CI) 1.00 to 1.15) and 1.10 (95% CI 1.01 to 1.18), respectively. In adjusted analyses there was no evidence of an increased risk of postoperative complications in the undirected group. However, the unadjusted ORs were higher for mortality (OR 1.35, 95% CI 1.26 to 1.44), failure to rescue (OR 1.15, 95% CI 1.08 to 1.24) and complications (OR 1.31 95% CI 1.28 to 1.45). Adjustment for differences in case-mix, co-morbidity and hospital characteristics accounted for much of the observed increased risk in outcomes. We assessed that co-morbidity had a high risk of imprecision and the remaining increased effect seen may have been due to residual confounding. See Analyses 3.1, 3.2 and 3.3 (Table 5).

DISCUSSION

Summary of main results

This review included six non-randomized studies (NRS) evaluating clinical outcomes when physician anaesthetists are compared with non-physicians, either working alone or in teams of various combinations. Overall, while some studies have shown small and inconsistent differences in some outcomes, the quality and nature

of the evidence are insufficient to draw firm conclusions about relative benefits and risks of the different models of anaesthetic provision. Perioperative risk is composed of three elements, the patient's pre-existing condition (for instance, the risk of pulmonary aspiration of gastric contents (Smith 1997)), the operation performed, and the perioperative care received, of which anaesthetic care is only one part. The included studies have not been able to successfully separate anaesthetic care from other risk factors.

Overall completeness and applicability of evidence

The included studies were mainly from the United States (US) and used routinely-collected administrative data. Only one study was carried out in the developing world. We found none from countries with advanced healthcare systems outside the US. Within the US, the data presented may not be representative as they may be skewed to the more deprived. Further, only billed cases were included, which raises the possibility of a systematic bias in the coverage of the data.

It is important to be aware of potential biases in the studies themselves. In the US, there are tensions between the official positions of the two professional organisations of the two main groups of anaesthesia providers, physician anaesthesiologists and registered nurse anaesthetists (Kane 2004). Some of the studies included in this review were funded, at least in part, by those professional organisations and were published in their own journals. Whilst this does not invalidate the results, it is unlikely that one group would publish work which weakened its own political position. The nature and small number of the studies included made it impossible to apply the usual methods used to detect publication bias (for instance, funnel plots) and this has to remain a possible source of bias.

Quality of the evidence

All studies were non-randomized and so are at considerable risk of bias due to the effects of confounding and selection bias. Further, as different studies took different approaches to definitions and adjustment, it was not possible to compare them directly. It was also problematic trying to fully control for differences in hospital characteristics, and especially for patient co-morbidity, using these routinely-collected data. It is open to speculation in which direction such confounding factors might be operating; in general, common sense would dictate that the skill levels of anaesthetic providers would be matched, where possible, to the complexity and riskiness of the patient's condition and the surgical procedure. As Needleman notes (p465), "The model of anaesthetic provision may be a proxy for other clinical resource variables usually left unmeasured in typically used databases" (Needleman 2009). Finally, no study assessed cost, length of hospital stay or the patient's perspective as an outcome.

Potential biases in the review process

We conducted a comprehensive search for material, including what is sometimes termed 'grey' literature (non-peer reviewed reports etc.). However, we did not access the grey literature database National Technical Information Service (NTIS), which may have potentially included more American literature.

We considered each eligible study with three independent reviewers and took time to understand the complexities of the American healthcare insurance system on which most of the studies were based. We sought advice from American peers, where necessary, and requested additional information from study authors who mostly responded promptly to our requests. Despite this, it is possible that our lack of intimate understanding of the American healthcare insurance system may have biased our interpretation of the included studies.

Agreements and disagreements with other studies or reviews

The only other review in this area which we are aware of is that of Smith (one of the authors on the present review) and colleagues from 2004 (Smith 2004). The present review has identified four studies published since 2004, and also excluded two studies which the 2004 review included. In addition, we used more recently developed, more sophisticated techniques for assessing risk of bias in non-randomized studies. There is little difference in the conclusions between the two reviews.

AUTHORS' CONCLUSIONS

Implications for practice

No definitive statement can be made about the possible superiority of one type of anaesthesia care over another. The complexity of perioperative care, the low intrinsic rate of complications relating directly to anaesthesia, and the potential confounding effects within the studies reviewed, all of which were non-randomized, make it impossible to provide a definitive answer to the review question.

Implications for research

A definitive answer to this question is unlikely. A randomized controlled trial is unlikely to be performed as it poses logistic difficulties in terms of allocation concealment and blinding of participants and personnel. Further, randomization may be unacceptable to health service providers, research ethics committees and

patients, particularly for high-risk patients and procedures. In the meantime, hospital data could be collected or processed to better enable individual patient analyses.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Dulisse 2010

Methods	Retrospective cohort study, also incorporating a controlled before and after study Data collected for years 1999-2005
Participants	All admissions in all Medicare surgical diagnosis-related groups (DRGs) for patients >65 years total of 481,440 hospitalizations. Day case surgery excluded Opt-in and opt-out states in US considered before and after opt-out occurred
Interventions	Based on Medicare part B claim reports • NPA working alone • physician anaesthetist working alone • team (defined as "team anesthesia in which anesthesiologists supervise or direct nurse anesthetists")
Outcomes	Outcomes based on Medicare discharge abstract • Inpatient mortality • Anaesthesia related complications (identified from patient safety indicators developed by Agency for Healthcare Research and Quality and including anaesthesia complications, death in low mortality diagnoses, failure to rescue, iatrogenic pneumothorax, postoperative metabolic and physiological derangement, postoperative respiratory failure, transfusion reaction). Analysed as single yes /no indicator if any of one of them occurred
Notes	Confounders considered for analysis: patient characteristics case-mix Methods used to adjust for confounders: multivariate logistic regression

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation and allocation concealment (selection bias)	High risk	NRS. Participants allocated on basis of time and location differences and decisions of healthcare decision makers
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Unclear risk	Risk of inaccuracy - MEDIUM. Assigned based on Medicare Part B forms. Cases with no Part B form were assigned to NPA team anaesthesia if the procedure took place in a "pass-through" hospital.Contribution and accuracy of pass through codes unclear

Dulisse 2010 (*Continued*)

Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	Risk of inaccuracy - LOW: Reporting of deaths is likely to be complete in medicare discharge abstract
Detection bias (accuracy with which outcomes assessed) - Serious airway complication	Unclear risk	Risk of inaccuracy - MEDIUM. Not clear what data source to identify complications. No details of how complete complications recording likely to be
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors link the two part of Medicare file data, but with no details of how this is done
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov). Due to high number of codes which could be selected for outcomes, it is unclear whether bias has been introduced without a protocol
Other bias	High risk	Funding sources: funded by American Association of Nurse Anesthetists (AANA). No details given of role of funder but statement that authors wholly responsible for data, analyses and conclusions

Needleman 2009

Methods	Retrospective cohort study Data from hospital discharge records Data collected for years 1999-2001
Participants	Obstetric patients for vaginal delivery or caesarean section.Data on 271,350 caesarean sections only extracted 369 hospitals in 6 states in US Age groups 12% <20 years; 14% ≥35 years; 74% 20-34 years
Interventions	Based on response to 2004 survey of hospitals • NPA alone • physician anaesthetist alone • NPA + physician anaesthetist (physician anaesthetist required at all c-sections): NPA + physician anaesthetist (physician anaesthetist *not* required at all c-sections) • Mixed - model varied
Outcomes	Based on hospital discharge data • Mortality - time period not specified • Anaesthesia complications (ICD 9 codes 668.0-668.2, 668.8 and 668.9) • Other complications - including cardiac complications, obstetrical shock, cardiac arrest, cerebral anoxia and other CV events and pulmonary complications • Obstetrical trauma

Notes	Confounders considered in analysis: Patient characteristics Hospital characteristics Methods used to adjust for confounders: Multivariate logistic regression Propensity matching Other notes: Information also taken from Minnick 2008 and Needleman 2010

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sequence generation and allocation concealment (selection bias)	High risk	NRS. Participants allocated based on location differences, health care decision makers and participant preference
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Unclear risk	Risk of inaccuracy - MEDIUM: Based on survey in 2004, after data for study collected. Only 34% response rate to original survey
Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	Risk of inaccuracy - LOW: mortality assessment likely to be accurate. Likely to be complete ascertainment
Detection bias (accuracy with which outcomes assessed) - Serious airway complication	High risk	Risk of inaccuracy - HIGH: Accuracy coding of discharge data may vary between hospitals and this may vary with provider model which could bias estimates
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors use discharge database. But unclear how complete the reporting of complication outcomes are on these databases
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov). Due to high number of codes which could be selected for outcomes, it is unclear whether bias has been introduced without a protocol
Other bias	High risk	Funding sources: funded by grant from Amercian Association of Nurse Anesthetists (AANA). No details of involvement of funder Other: Only hospitals that replied to orig-

		inal survey included, only 34% response rate

Pine 2003

Methods	Retrospective cohort study Data collected 1995-1997
Participants	404,194 patients who underwent elective surgery; carotid endarterectomy, cholecystectomy, herniorrhaphy, hysterectomy, knee replacement, laminectomy, mastectomy, prostatectomy. Patients all > 65 years 1177 hospitals in 22 states in US Hospitals included from both urban and rural locations, with different technological sophistication
Interventions	Data from Medicare part B claim reports • NPA alone • physician anaesthetist working alone • Team (physician anaesthetist and NPA)
Outcomes	Data from Medicare - unclear whether Form A or B • Mortality before discharge
Notes	Confounders considered in analysis: Patient case-mix Co-morbidity Hospital characteristics Methods used to adjust for confounders: Indirect standardisation; C-statistic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sequence generation and allocation concealment (selection bias)	Unclear risk	NRS. Participants allocated based on location differences and health care decision makers
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Low risk	Risk of inaccuracy - LOW: High exclusion of cases with unclear provider data
Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	Risk of inaccuracy - LOW: mortality assessment likely to be accurate. Likely to be complete ascertainment

Pine 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors link the two part of Medicare file data, but with no details of how this is done
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov)
Other bias	Low risk	Funding sources: None apparent

Rosseel 2010

Methods	Cohort study - unclear if retrospective or prospective Data taken from a health emergency following a series of hurricanes in 2008
Participants	330 participants undergoing emergency procedures including obstetrical, trauma, and non-trauma operations GA without intubation; GA with intubation; spinal anaesthesia; other Median patient age 27yrs (interquartile range 17-38 yrs)
Interventions	• NPA working without supervision • NPA supervised by physician anaesthetist
Outcomes	• perioperative mortality rate
Notes	Confounders considered in analysis: None Other notes: Email contact with author to clarify that data for mortality rates, supplied in the paper, was for a nurse anaesthetist supervised by a physician anaesthetist Data also supplied for local anaesthetic and no anaesthetic. These data not included in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sequence generation and allocation concealment (selection bias)	High risk	NRS. Participants allocated based on health care decision makers and availability of personnel
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Unclear risk	No details of how original data has been recorded
Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	No details given in paper about detection but likely to be low risk

Rosseel 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	330 participants within one surgical unit
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov)
Other bias	High risk	Funding sources: No statement but authors funded by MSF who organized NPA training programme

Silber 2000a

Methods	Retrospective cohort study Data collected 1991-1994 Data from Medicare part B claims reports. Also use of American Hospital Association Annual Surveys, and the Pennsylvania Health Care Cost Containment Council Data Base
Participants	217,740 patients undergoing general surgical procedures or orthopedic procedures 245 hospitals in Pensylvania in US Patients all over 65 years
Interventions	Data from Medicare part B form • NPA undirected: includes supervised by physician anaesthetist or directed by non-anaesthetist physician, Unbilled cases included in this group • NPA directed: included directed by physician anaesthetist or physician anaesthetist alone
Outcomes	Data from HFCA database and vital status file • Death within 30 days of admission • Complications. Unclear time period. Any one of from a list of 41 events including all cardiac, respiratory and gastro-intestinal systems • Failure to rescue. Defined as 30 day death rate in those in whom either a complication developed or died without a complication being recorded
Notes	Confounders considered in analysis: patient characteristics Hospital characteristics Methods used to adjust for confounders: Mantel Haenszel adjustments Propensity scores Other notes: Also reported in Silber 2000b

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Silber 2000a (*Continued*)

Sequence generation and allocation concealment (selection bias)	High risk	NRS. Participants allocated on basis of time and location differences and decisions of healthcare decision makers
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Unclear risk	Risk of inaccuracy - MEDIUM: undirected group includes large number of unbilled cases but sensitivity analyses with these cases removed gave same results. Participants with multiple anaesthetics in one admission classed as undirected if any single procedure in a day was undirected
Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	Risk of inaccuracy - LOW: mortality assessment likely to be accurate. Likely to be complete ascertainment
Detection bias (accuracy with which outcomes assessed) - Failure to rescue	Unclear risk	Unclear: New complications poorly differentiated from existing co-morbidities
Detection bias (accuracy with which outcomes assessed) - Serious airway complication	Unclear risk	Risk of inaccuracy - Unclear: not clear how new complications were differentiated from existing co-morbidities
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors use several data sources, e.g. HFCA vital status file, Medicare part B. Unclear how these were linked
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov). Due to high number of codes which could be selected for outcomes, it is unclear whether bias has been introduced without a protocol
Other bias	Unclear risk	Funding sources: Largely self-funded. Background methodology work supported by grants from Agency of Healthcare research and Quality (AHRQ) and American Board of Anesthesiology

Simonson 2007

Methods	Retrospective cohort study Data collected 1993-2004
Participants	134, 806 patients undergoing caesarean section 68 hospitals in Washington state in US
Interventions	Based on data from hospital surveys • NPA alone: at least 90% of cases in hospital performed by NPA working alone • physician anaesthetist alone: at least 90% of cases hospital performed by physician anaesthetist working alone
Outcomes	Based on Comprehensive Hospital Abstract and Reporting System • Mortality - time period not specified • Anaesthetic complications - based on ICD9 668.0 to 668.9 and including patient safety indicators for anaesthesia
Notes	Confounders considered in analysis: Patient characteristics Co-morbidity Hospital characteristics Methods used to adjust for confounders: Hierarchical multivariate logistic model

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation and allocation concealment (selection bias)	High risk	NRS. Participants allocated based on location differences, health care decision makers and participant preference
Performance bias. All outcomes	High risk	Not possible to blind personnel
Accuracy with which intervention or control group determined (risk of misclassification)	Unclear risk	Risk of inaccuracy - MEDIUM: Intervention/ comparison group assigned at hospital level based on survey completed by anaesthesia providers or administrators. Hospital allocation varied over time
Detection bias (accuracy with which outcomes assessed) - Mortality	Low risk	Risk of inaccuracy - LOW: mortality assessment likely to be accurate. Likely to be complete ascertainment
Detection bias (accuracy with which outcomes assessed) - Serious airway complication	High risk	Risk of inaccuracy - HIGH: Accuracy coding of discharge data may vary between hospitals and this may vary with provider model which could bias estimates

Simonson 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors use CHARS database for outcome data. But unclear how complete the reporting of complication outcomes are on these databases
Selective reporting, *a priori* protocol, *a priori* analysis plan (reporting bias)	Unclear risk	No published protocol found (to include search of clinicaltrials.gov). Due to high number of codes which could be selected for outcomes, it is unclear whether bias has been introduced without a protocol
Other bias	Low risk	Funding sources: No apparent funding support

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

Study	Reason for exclusion
Abouleish 2004	There no surgical patients in this study. All epidurals for vaginal delivery
Charuluxananan 2005	No details of whether nurse anaesthetists are supervised or not. Outcomes not analysed by provider type
Charuluxananan 2008	There were no NPAs working independently
Faponle 2004	Unclear whether nurse anaesthetists were working unsupervised. Successful contact made with author confirmed that all nurse anaesthetists were supervised by consultant anaesthetists
Fleming 1992	Unclear whether nurse anaesthetists were working unsupervised. Successful contact made with author but due to length of time since published, no records available to confirm this query
Hoffmann 2002	There were no NPAs working independently
Leonard 2012	Unclear whether physician assistants (NPAs) were working unsupervised. Successful contact made with author confirmed that all physician assistants were supervised within a team
Maaløe 2000	There were no NPAs working independently

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

Carpentier 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	French study. Query over whether nurse anaesthetist (NPA) is working unsupervised. Contact made with author. Awaiting reply

DePaolis-Lutzo 1995

Methods	No details
Participants	
Interventions	
Outcomes	
Notes	Unable to source abstract or full text. Title only available from search results. No author contact details

Ezedigboh 1999

Methods	No details
Participants	
Interventions	
Outcomes	
Notes	Unable to source abstract or full text. Title only available from search results

Gadir 2007

Methods	Retrospective and prospective cohort study Data collected 1998-2001
Participants	55,834 participants. Procedures not specified Two individual hospitals and a group of hospitals from Sudanese states
Interventions	Data based on hospital records. Data from states hospitals taken from personal communications with surgeons and anaesthetic assistants where no records available • unsupervised anaesthesia assistants

Gadir 2007 (*Continued*)

	• physician anaesthetist • supervised anaesthesia assistants
Outcomes	Morbidity and mortality
Notes	No denominator data provided in the paper. Email request sent to study authors. Awaiting reply

Goldman 1988

Methods	No details
Participants	
Interventions	
Outcomes	
Notes	Unable to source abstract or full text. Title only available from search results

MacKenzie 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to source abstract of full text. Email sent to journal to request a copy before assessing for eligibility. Awaiting reply

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Analysis 1.1. Comparison 1: mortality

Study ID	Study population	Unadjusted results			Adjusted results			Confounders included
		Effect measure	NPA alone	Physician anaesthetist alone	Effect measure	NPA alone	Physician anaesthetist alone	
Needleman 2009	Obstetric patients, caesareans	Risk difference (1/10,000) compared to physician anaesthetist alone	-1.45	0	Odds ratio (reference = physician anaesthetist alone)	0.556	1	Co-morbidity and hospital characteristics
Simonson 2007	Obstetric patients, caesareans	Events/ total (Risk /10,000)	4/33,236 (1.20)	13/101,570 (1.28)	/	/	/	Co-morbidity and hospital characteristics
Dulisse 2010	Surgical				Odds ratio (reference = physician anaesthetist alone in non opt out states)			
Non opt out		/	/	/		0.899*	1	Case-mix and co-morbidity
Opt out -before						0.651*	0.797*	
Opt out-after						0.689*	0.788*	
Pine 2003	Surgical	/	/	/	Events/total (Risk/10,000) SMR - standardised to whole study	13/101,570 (46) 1.031	604/134,335 (45) 1.039	Case-mix, co-morbidity and hospital characteristics

Table 1. Analysis 1.1. Comparison 1: mortality (*Continued*)

					population			

* significant difference reported by study authors P = 0.05

Table 2. Analysis 1.2. Comparison 1: complications

Study ID	Study population	Unadjusted results			Adjusted results			Confounders included
		Effect measure	NPA alone	Physician anaesthetist alone	Effect measure	NPA alone	Physician anaesthetist alone	
Needleman 2009	Obstetric patients, caesareans	Rate difference (1/10,000) compared to physician anaesthetist alone	-6.0	0	Odds ratio (reference = physician anaesthetist alone)	0.732	1	Co-morbidity and hospital characteristics
Simonson 2007	Obstetric patients, caesareans	Events/total (Risk /10,000)	192/33,236 (57.8)	773/101,570 (76.1)	Odds ratio (reference = physician anaesthetist alone)	1.046 (95% CI 0.649-1.685)	1	Co-morbidity and hospital characteristics
Dulisse 2010	Surgical							
Non-opt out		/	/	/	Odds ratio (reference = physician anaesthetist alone in non-opt out states)	0.992	1	Case-mix and co-morbidity
Opt out - before						0.798*	0.824*	
Opt out - after						0.927	0.818*	

* significant difference reported by study authors P = 0.05
CI (confidence interval)

Table 3. Analysis 2.1. Comparison 2: mortality

Study ID	Study population	Comparison group	Unadjusted results			Adjusted results			Confounders included
			Effect measure	NPA alone	NPA supervised	Effect measure	NPA alone	NPA supervised	
Needleman 2009	Obstetric patients, caesareans	Physician anaesthetist present at all c-sections	Rate difference (1/10,000) compared to Physician anaesthetist only	-1.45	-0.54	Odds ratio (reference = Physician anaesthetist alone)	0.556	0.708	Co-morbidity and hospital characteristics
		Physician anaesthetist not present at all c-sections		-1.45	-0.61		0.556	0.716	
Dulisse 2010	Surgical								
Non opt out		Team	/	/	/	Odds ratio (reference = Physician anaesthetist alone in non opt out states)	0.899*	0.959*	Case-mix and co-morbidity
Opt out - before		Team					0.651*	0.708*	
Opt out - after		Team					0.689*	0.565*	
Pine 2003	Surgical	Team				Events/ total (Risk /10,000) SMR - standardised to whole study population	151/33, 151 (46) 1.031	796/236, 708 (34) 0.967	Case-mix, co-morbidity and hospital characteristics
Rosseel 2010	Surgical	Physician anaesthetist supervision	Events/ total	0/168	1/162	/	/	/	/

* significant difference reported by study authors P = 0.05

Table 4. Analysis 2.2. Comparison 2: complications

Study ID	Study population	Comparison group	Unadjusted results			Adjusted results			Confounders included
			Effect measure	NPA alone	NPA supervised	Effect measure	NPA alone	NPA supervised	
Needleman 2009	Obstetric patients, caesareans	Physician anaesthetist present at all caesareans	Rate difference (1/10,000) compared to Physician anaesthetist only	-6.0	-11.0	Odds ratio (reference = Physician anaesthetist alone)	0.732	0.832	Co-morbidity and hospital characteristics
		Physician anaesthetist not present at all caesareans		-6.0	-2.0		0.732	0.922	
Dulisse 2010	Surgical								
Non opt out		Team	/	/	/	Odds ratio (reference = Physician anaesthetist alone in non opt out states)	0.992	1.67*	Case-mix, co-morbidity and hospital characteristics
Opt out - before		Team					0.798*	0.927	
Opt out-after		Team					0.927	0.903	

* significant difference reported by study authors P = 0.05

Table 5. Analysis 3.1. Comparison 3: mortality

Study ID	Study population	Unadjusted results			Adjusted results			Confounders included
		Effect measure	Undirected NPA	Directed NPA	Effect measure	Undirected NPA	Directed NPA	
Silber 2000a	Surgical	Odds ratio (reference - directed NPA)	1.35 (95% CI 1.26 to 1.44)	1	Odds ratio (reference - directed NPA)	1.08 (95% CI 1.00-1.15)	1	Case-mix, co-morbidity and hospital charac-

Table 5. Analysis 3.1. Comparison 3: mortality (*Continued*)

								teristics

CI (Confidence Interval)

APPENDICES

Appendix 1. Physician anaesthetist versus non-physician providers of anaesthesia as defined in this study

Medically qualified: physician anaesthetist	
Anaesthetist	Sometimes called anesthetist
Anesthesiologist	Term used in, although not unique to, US. Also called anaesthesiologist
Non-physician anaesthetist	
CRNA	Certified Registered Nurse Anesthetist. Specific to US. Specially trained to administer all anaesthetics. In most US states will work under supervision. CRNAs are allowed to work unsupervised in 16 states. Can be referred to as anesthetists in US literature
Nurse anaesthetists	Involved in some anaesthetic procedures. Provide supervised assistance within a team
Circulation nurses	Involved in preparation of anaesthetic drugs. Provide supervised assistance within a team
PA(A)	Physician assistants (anaesthesia). Previously called anaesthetic physician assistants (APA). Involved in induction of anaesthetics to ASA 1 & 11 patients. Supervised
Clinical officers	Work in developing world. Responsibilities vary
Theatre practitioner (with extended role)	May have training to assist specifically within anaesthetic team

(*Continued*)

Personnel unlikely to administer anaesthetic	
Anaesthesia technicians Anesthesiology assistants	Responsible for preparing operating theatre, checking machinery etc Provide supervised assistance to anesthesiologist

Appendix 2. Search strategies

	MEDLINE (via Ovid)
1	exp *Anesthesia/ or exp *Anesthesiology/ or an?esth*.ti.
2	(CRNA* or certified registered nurse an?esth*).mp.
3	exp Nurse Anesthetists/
4	nurse an?esthetist*.mp.
5	((nurs* or assistant* or technician* or officer*) adj3 (anaesth* or anesth*)).mp
6	((mid-level adj3 provider*) or advanced registered nurse practitioner* or clinical officer*).mp
7	1 and 6
8	(physician adj3 (extender* or assistant*)).mp. or exp Physician Assistants/ or Physician Assistant*.mp
9	1 and 8
10	(non-physician an?esth* or non physician an?esth*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11	((non-physician adj3 an?esthetist*) or (non physician adj3 an?esthetist)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12	anesthesia nursing.mp.
13	exp perioperative nursing/
14	perioperative nursing.mp.
15	exp physician-nurse relations/

(*Continued*)

16	physician-nurse relations.mp.
17	operating department practitioner*.mp.
18	patient care team.mp.
19	exp Patient Care Team/
20	exp Operating Room Technicians/
21	operating room technicians.mp.
22	exp Health Personnel/
23	health personnel.mp.
24	exp Health Manpower/
25	health manpower.mp.
26	exp Nursing/
27	nursing.mp.
28	2 or 3 or 4 or 5 or 7 or 9 or 10 or 11 or 12
29	or/13-27
30	1 or 29
31	28 and 30

	EMBASE (via Ovid)
1	exp *Anesthesia/ or exp *Anesthesiology/ or an?esth*.ti.
2	(CRNA* or certified registered nurse an?esth*).mp.
3	exp Nurse Anesthetists/
4	nurse an?esthetist*.mp.
5	((nurs* or assistant* or technician* or officer*) adj3 (anaesth* or anesth*)).mp

(*Continued*)

6	((mid-level adj3 provider*) or advanced registered nurse practitioner* or clinical officer*).mp
7	1 and 6
8	(physician adj3 (extender* or assistant*)).mp. or exp Physician Assistants/ or Physician Assistant*.mp
9	1 and 8
10	(non-physician an?esth* or non physician an?esth*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11	((non-physician or non physician) adj3 an?esthetist*).mp.
12	exp anesthesia nursing/
13	anesthesia nursing.mp.
14	exp nurse-doctor relations/
15	nurse-doctor relations.mp.
16	operating department practitioner*.mp.
17	patient care.mp.
18	exp Patient Care/
19	exp Operating Room Personnel/
20	operating room personnel.mp.
21	exp Health Care Personnel/
22	health care personnel.mp.
23	exp Health Care Manpower/
24	health care manpower.mp.
25	exp Nursing/
26	nursing.mp.
27	2 or 3 or 4 or 5 or 7 or 9 or 10 or 11 or 12 or 13
28	or/14-26

(*Continued*)

29	1 or 28
30	27 and 29

CINAHL via EBSCO	
S1	(MH "Anesthesia+") OR (MM "Anesthesiology") OR (TI anesth* OR anaesth*)
S2	CRNA* OR (certified registered nurse an#esth*)
S3	(MH "Nurse Anesthetists")
S4	(nurse anesthetist*) OR (nurse anaesthetist*)
S5	(nurs* OR assistant* OR technician* OR officer*) N3 (anesth* OR anaesth*)
S6	((mid-level N3 provider*) OR advanced registered nurse practitioner* OR clinical officer*)
S7	S1 AND S6
S8	(physician N3 (extender* OR assistant*)) OR physician assistant* OR (MM "Physician Assistants")
S9	S1 AND S8
S10	operating department practitioner
S11	(MH "Multidisciplinary Care Team+")
S12	multidisciplinary care team
S13	(MH "Operating Room Personnel+")
S14	operating room personnel
S15	(MH "Health Personnel+")
S16	health personnel
S17	(MH "Health Manpower+")
S18	health manpower
S19	(MH "Perioperative Nursing")
S20	perioperative nursing

(*Continued*)

S21	(non-physician or non physician) N3 (anaesthetist* or anesthetist*)
S22	(non-physician anesthetist) OR (non-physician anaesthetist) OR (non physician anesthetist) OR (non physician anaesthetist)
S23	(MH "Anesthesia Nursing")
S24	anesthesia nursing
S25	(MH "Nurse-Physician Relations")
S26	nurse-physician relations
S27	S2 OR S3 OR S4 OR S5 OR S7 OR S9 OR S21 OR S22 OR S23 OR S24
S28	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S25 OR S26
S29	S1 OR S28
S30	S27 AND S29

CENTRAL	
#1	MeSH descriptor: [Anesthesia] explode all trees
#2	MeSH descriptor: [Anesthesiology] explode all trees
#3	anesth* or anaesth*:ti (Word variations have been searched)
#4	#1 or #2 or #3
#5	CRNA* or (certified registered nurse anesthetist*)
#6	MeSH descriptor: [Nurse Anesthetists] explode all trees
#7	(nurse anesthetist) or (nurse anaesthetist)
#8	((nurs* or assistant* or technician* or officer*) near/3 (anesth* or anaesth*))
#9	(mid-level near/3 provider*) or (advanced registered nurse practitioner*) or (clinical officer*)
#10	#4 and #9

(*Continued*)

#11	(physician near/3 (extender* or assistant*)) or (physician assistant)
#12	MeSH descriptor: [Physician Assistants] explode all trees
#13	#11 or #12
#14	#4 and #13
#15	(non-physician anaesth*) or (non-physician anesth*) or (non physician anaesth*) or (non physician anesth*)
#16	(non-physician near/3 (anaesth* or anesth*) or non physician near/3 (anaesth* or anesth*))
#17	MeSH descriptor: [Physician-Nurse Relations] explode all trees
#18	nurse-physician relations
#19	operating department practitioner
#20	MeSH descriptor: [Patient Care Team] explode all trees
#21	patient care team
#22	MeSH descriptor: [Operating Room Technicians] explode all trees
#23	operating room technicians
#24	MeSH descriptor: [Health Personnel] explode all trees
#25	health personnel
#26	MeSH descriptor: [Health Manpower] explode all trees
#27	health manpower
#28	MeSH descriptor: [Nursing Staff] explode all trees
#29	nursing staff
#30	#5 or #6 or #7 or #8 or #10 or #14 or #15 or #16
#31	#17 or #18 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#32	#4 or #31
#33	#30 and #32 from 2013 to 2014

Appendix 3. Data extraction form - RCTs

Data Collection Form - RCTs

Review title or ID

Study ID *(surname of first author and year first full report of study 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 that data extracted from)	
Report ID (ID for this paper/ abstract/ report)	

(*Continued*)

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**	**Yes** **No** **Unclear**	**Location in text** *(pg & ¶ /fig / table)*
Type of study	Randomized Controlled Trials		
Participants	General, spinal or epidural anaesthetic. Hospital setting		
Types of intervention	Anaesthetic given by NPA working independently.		
Types of comparisons	Anaesthetic given by anaesthetist working independently. Anaesthetic given by anaesthetist working as part of a team. Anaesthetic given by NPA working as part of a team.		
Types of outcome measures	Mortality from GA within 30 days. Complications from GA.		

(*Continued*)

	Patient reported satisfaction		
INCLUDE	**EXCLUDE**		
Reason for exclusion			
Notes:			

DO NOT PROCEED IF EXCLUDED FROM REVIEW

3. Population and setting

	Description *(include comparative information for each group (i.e. intervention and controls) if available*	**Location in text (pg & ¶ /fig / table)**
Population and description *(from which study participants are drawn)*		
Setting *(including country, rural/urban 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 *(pg & ¶ /fig / table*
Aim of study		
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

Domain	Risk of bias High Low Unclear	Support for judgement	Location in text *(pg & ¶ /fig / table*
Random sequence generation *(selection bias)*			
Allocation concealment *(selection bias)*			
Blinding of participants and personnel *(performance bias)*		**Primary outcomes: mortality**	
		Primary outcome: complications from GA	
		Patient reported satisfaction	
Blinding of outcome assessment *(detection bias)*		**Primary outcome: mortality**	
		Primary outcome: complication from GA	

(*Continued*)

		Patient reported satisfaction	
Incomplete outcome data *(attrition bias)*		**Mortality**	
		Complications from GA	
		Patient reported satisfaction	
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** *(pg & ¶ /fig / table*
Total no. randomized		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		

(*Continued*)

Race/Ethnicity		
Severity of illness *(e.g. ASA I or II)*		
Co-morbidities		
Other treatment received		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

7.1 Intervention group *(repeat as necessary)*

	Description as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Intervention *(e.g. anaesthetic given by NPA working independently)*		
Type of anaesthetic *(general, spinal, epidural or mix)*		
Type of surgical procedure and method		
No. randomized to group *(specify whether no. people or clusters)*		
Experience & training of NPA		
Role & specific responsibilities of NPA		

(*Continued*)

Duration of treatment period		
Other providers in theatre *(e.g. surgeon, nurse practitioners)*		
Co-interventions		
Notes:		

8.1 Outcomes *(repeat as necessary)*

	Description as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome tool validated? **Yes No Unclear**		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		

(*Continued*)

Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power		
Notes:		

9.1 Results - dichotomous results *(repeat as necessary)*

	Description as stated in report/paper				**Location in text** *(pg & ¶ /fig / table*
Comparison					
Outcome					
Subgroup					
Timepoint *(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					

(*Continued*)

Unit of analysis *(by individuals, cluster/ groups or body parts)*			
Statistical methods used & appropriateness of these methods *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	**Yes No Unclear**		
Reanalysis possible?	**Yes No Unclear**		
Reanalysed results			
Notes:			

9.2. Results - continuous data *(repeat as necessary)*

	Description as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Comparison		
Outcome		
Subgroup		

(*Continued*)

Timepoint *(specify whether from start or end of intervention)*		
Post-intervention or change from baseline?		
Results **Intervention** Mean SD (or other variance) No. Participants		
Results **Comparison** Mean SD (or other variance) 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 & 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 population groups been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	**Yes No Unclear**
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** *(pg & ¶ /fig / table*
Key conclusion of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

END

Data Collection Form - NRS

Review title or ID

Study ID *(surname of first author and year first full report of study 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 that data extracted from)	
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)	

(*Continued*)

Notes:	

2.1 Study Eligibility

Study Characteristics	**Eligibility criteria**	**Yes**	**No**	**Unclear**	**Location in text** *(pg & ¶ /fig / table)*
Participants	General, spinal or epidural anaesthetic. Hospital setting				
Types of intervention	Anaesthetic given by NPA working independently.				
Types of comparisons	Anaesthetic given by anaesthetist working independently. Anaesthetic given by anaesthetist working as part of a team. Anaesthetic given by NPA working as part of a team.				
Types of outcome measures	Mortality from GA within 30 days. Complications from GA. Patient reported satisfaction				

2.2 Study design features - individual. (*Additional explanatory notes available on request from authors*)
List of study design features (for studies formed by classifying participants according to whether they received the intervention or comparator): individual-level group formation

	Yes	No	Can't tell	N/A
Was there a relevant comparison:				
Between two or more groups of participants receiving different interventions?				
Within the same group of participants over time?				
Were groups formed by:				
Randomization?				
Quasi-randomization?				
Other action of researchers?				
Time differences?				
Location differences?				
Health care decision makers?				
Participants' preferences?				
On the basis of outcome?				
Some other process (specify)?				
Were the features of the study described below carried out after the study was designed?				
Identification of participants				

(*Continued*)

Assessment before intervention				
Actions/choices leading to an individual becoming a member of a group				
Assessment of outcomes				
On what variables was comparability of groups assessed?				
Potential confounders				
Assessment of outcomes before intervention				

Ideally, review authors should record the basis for their judgements (e.g. by quotations from the text of a paper), as they do when assessing the risk of bias.

2.3 Study design features - cluster (*Additional explanatory notes available on request from authors)*

List of study design features (studies formed by classifying clusters by intervention and comparator): individual-level group formation

	Yes	No	Can't tell	N/A
Was there a relevant comparison:				
Between two or more groups of participants receiving different interventions?				
Within the same group of participants over time?				
Were groups formed by:				
Randomization?				
Quasi-randomization?				

(*Continued*)

Other action of researchers?				
Time differences?				
Location differences?				
Health care decision makers?				
Participants' preferences?				
On the basis of outcome?				
Some other process (specify)?				
Were the features of the study described below carried out after the study was designed?				
Identification of participants				
Assessment before intervention				
Actions/choices leading to an individual becoming a member of a group				
Assessment of outcomes				
On what variables was comparability of groups assessed?				
Potential confounders				
Assessment of outcomes before intervention				

Note that 'cluster' refers to an entity (e.g. an organization), not necessarily to a group of participants; 'group' in a cluster-allocated study refers to one or more clusters.

Ideally, review authors should record the basis for their judgements (e.g. by quotations from the text of a paper), as they do when assessing the risk of bias.

2.4 Eligibility decision

Include /Exclude
Reason for exclusion
Notes:

DO NOT PROCEED IF EXCLUDED FROM REVIEW

3. Population and setting

	Description *(include comparative information for each group (i.e. intervention and controls) if available*	**Potential source of bias?** *(tick then add to section 8)*	**Location in text** *(pg & ¶ /fig / table)*
Population and description *(from which study participants are drawn)*			
Setting *(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	Potential source of bias? *(tick then add to section 8)*	Location in text *(pg & ¶ /fig / table*
Aim of study			
Design *(e.g. parallel, crossover, 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. Participants

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

	Description as stated in report/paper	Potential source of bias? *(tick then add to section 8)*	Location in text *(pg & ¶ /fig / table*
Total no. participants			
Clusters *(if applicable, no., type, no. people per cluster)*			
Withdrawals and exclusions *(if not provided below by outcome)*			
Age			
Sex			
Race/Ethnicity			
Severity of illness *(e.g. ASA I or II)*			
Co-morbidities			
Other treatment received			
Other relevant sociodemographics			
Subgroups measured			
Subgroups reported			
Notes:			

6.1 Intervention group

	Description as stated in report/paper	Location in text *(pg & ¶ /fig / table*
Intervention *(e.g.Anaesthetic given by NPA working independently)*		
Type of anaesthetic *(general, spinal, epidural)*		
Type of surgical procedure and method		
No. in group *(specify whether no. people or clusters)*		
Data source used to assign participants to group		
Training and experience of NPA		
Duration of treatment period		
Other providers in theatre *(e.g. surgeon, nurse practitioners)*		
Co-interventions		
Notes:		

7.1 Outcomes *(repeat as necessary)*

	Description as stated in report/ paper	Location in text *(pg & ¶ /fig / table*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Data source used for outcome ascertainment		
Unit of measurement		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome tool validated?	**Yes No Unclear**	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power		
Notes:		

(*Continued*)

8.1 Confounding

Assessment of how researchers dealt with confounding	
Method for *identifying* relevant confounders described by researchers: Yes No If yes, describe the method used:	
Relevant confounders described: Yes No List confounders described below	
Method used for controlling for confounding At design stage: matching by characteristics of subjects (see below for matching by propensity score) Variables on which subjects matched: …… …… …… …… At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression) Describe confounders controlled for below	

Confounders described by researchers

Enter / preprint prespecified list of confounders (rank order in importance? Important in bold?)
Tick (yes/no judgement) if confounder considered by the researchers [Cons'd?]
Score (1 to 5) precision with which confounder measured
Score (1 to 5) imbalance between groups
Score (1 to 5) care with which adjustment for confounder was carried out.

Confounder	Considered	Precision	Imbalance	Adjustment
Case-mix	Y/N	/5	/5	/5
Co-morbidity	Y/N	/5	/5	/5
Type of surgical procedure	Y/N	/5	/5	/5
Type of anaesthetic	Y/N	/5	/5	/5
Hospital characteristics	Y/N	/5	/5	/5
	Y/N	/5	/5	/5
	Y/N	/5	/5	/5

9.1 Results - dichotomous outcomes *(repeat as necessary)*

	Description as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Comparison		
Outcome		
Subgroup		
Timepoint *(specify whether from start or end of intervention)*		
No. missing participants and reasons		
No. participants moved from other group and reasons		

Unadjusted results	Intervention	Comparison	
Number of events			
Number of participants			
Unadjusted summary results			

Adjusted results reported - 1	Intervention	Comparison	
Number of events			
Number of participants			
Adjusted summary results			
Confounders adjusted for			

Adjusted results reported - 2	Intervention	Comparison	
Number of events			
Number of participants			
Adjusted summary results			
Confounders adjusted for			

Reanalysis required? *(specify)*	**Yes No Unclear**	
Reanalysis possible? Reanalysed results	**Yes No Unclear**	
Notes:		

9.2 Results - continuous outcomes

	Description as stated in report/paper	Location in text *(pg & ¶ /fig / table*
Comparison		
Outcome		
Subgroup		
Timepoint *(specify whether from start or end of intervention)*		
No. missing participants and reasons		
No. participants moved from other group and reasons		
Unadjusted results	**Intervention** **Mean** **SD** **No.**	**Comparison** **Mean** **SD** **No.**
Unadjusted summary results		
Adjusted results reported - 1	**Intervention** **Mean** **SD** **No.**	**Comparison** **Mean** **SD** **No.**
Adjusted summary results		
Confounders adjusted for		
Adjusted results reported - 2	**Intervention** **Mean** **SD** **No.**	**Comparison** **Mean** **SD** **No.**
Adjusted summary results		
Confounders adjusted for		
Reanalysis required? *(specify)*	**Yes No Unclear**	
Reanalysis possible?	**Yes No Unclear**	

(*Continued*)

Reanalysed results		
Notes:		

10. Bias assessment *(additional explanatory notes available on request from authors)*
Risk of bias table (non-randomized studies)

Item	**Judgement**[a]	**Description** (quote from paper, or describe key information)
1. Sequence generation		
2. Allocation concealment		
3. Confounding[b] **Mortality**		
Complication from GA		
Patient satisfaction		
4. Blinding? **Mortality**		
Complication from GA		
Patient satisfaction		
5. Incomplete outcome data addressed? **Mortality**		
Complication from GA		

(*Continued*)

Patient satisfaction		
6. Free of selective reporting? **Mortality**		
Complication from GA		
Patient satisfaction		
7. Free of other bias?		
8. *A priori* protocol?[c]		
9. *A priori* analysis plan?[d]		

[a] Some items on low/high risk/unclear scale (double-line border), some on 5 point scale/unclear (single line border), some on yes/no/unclear scale (dashed border). For all items, record "unclear" if inadequate reporting prevents a judgement being made.
[b] Based on list of confounders considered important at the outset and defined in the protocol for the review
[c] Did the researchers write a protocol defining the study population, intervention and comparator, primary and other outcomes, data collection methods, etc. in advance of starting the study? N.B. May be outcome specific.
[d] Did the researchers have an analysis plan defining the primary and other outcomes, statistical methods, subgroup analyses, etc. in advance of starting the study?

11. Applicability

Have important population groups been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	**Yes No Unclear**	
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	**Yes No Unclear**	

(*Continued*)

Does the study directly address the review question? *(any issues of partial or indirect applicability)*	**Yes No Unclear**	
Notes:		

12. Other information

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

Appendix 4. Table of confounders

Dulisse 2010	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	Yes	Yes	No	No
Data used	Medicare part A data	Medicare data		
Variable used	DRGs + base units* for most complicated anaesthetic procedure for each admission	Age, sex and race		
Risk of imprecision	**Low**	**High** No ASA or individual data		
Risk of imbalance	**High** Base units higher in PA cases	**Medium** Differences in percentage of African-American patients only base-line difference noted		
Analysis method	Mortality rates standardised to NPA case mix for case-type which both physician anaesthetist and NPA performed Multivariate logistic regression - including DRGs, base-units, age, sex and race			
Risk of incomplete adjustment	**Low** Good adjustment with available data			

* value for each anaesthesia code that reflects all activities other than anaesthesia time.

Needleman 2009	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	Yes all caesarean sections	Yes	No	Yes
Data used		Discharge data		Authors 2004 hospital survey & American Hospital Association survey
Variables		Age, ethnicity, Charlson score, 13 obstetrical comorbidities (maternal infection, maternal diabetes, maternal obesity,		anaesthetist continuously available, labor, delivery and recovery all in same room, location of nonemergency caesareans, number of person-

(*Continued*)

		fetal problems affecting mother, grand multiparity, elderly primagravida or multigravida, abnormal fetal HR, uterine rupture, long labour, obstructed labour, umbilical cord complication, other maternal complications, insufficient prenatal care), early onset labour		nel at caesareans, minutes to transfer to emergency caesarean delivery, births/ year, metropolitan location, ownership, teaching status, obstetric care level, no of neonatal intensive care beds/1000 births, state, year
Risk of imprecision	**Low**	**Medium** Very likely that coded abstract does not include all relevant information - as many will be secondary diagnoses Corrected in 2010 paper to include more co-morbidity codes which increased prevalence of diabetes and obesity		**Medium**
Risk of imbalance	**Low**	**Unclear** No details given of imbalance in participants		**High** No details given in main paper but Minnick 2008 suggests substantial differences
Analysis method	Multivariate log regression/propensity matching **Propensity score** created from: patient age, payer, ethnicity, maternal Charlson score, categorical variable for each component of Charlson score, early onset labour, metropolitan location			
Risk of incomplete adjustment	**Medium** No unadjusted rates given No numbers of events/denominators to assess model No strategy for model building			

Pine 2003	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	Yes	Yes		Yes

(*Continued*)

Data used	Medicare database	Medicare database		1997 American hospital annual surveys
Variables used	8 procedures only considered. Selected information about procedures, e.g. laparoscopic versus abdominal surgery	Age, sex, principal and secondary diagnoses.		Hospital: number of beds, average daily census, total no of inpatient operations, percentage of registered nurses, teaching status, location , technological sophistication
Risk of imprecision	**Low** homogenous populations	**Medium** Authors excluded secondary diagnoses coded more frequently as complications than as comorbid conditions (using SPARCS database*)		**Medium**
Risk of imbalance	**High** Large differences - percentage performed by NPA alone varies 2.6% endarterectomy to 13% for cholecystectomy	**Unclear** No details give		**High** Not fully presented but large differences in percentages of NPAs by state and rural location
Analysis method	Mortality rates presented indirectly standardised to whole population. Expected mortality rates calculated using stepwise logistic regression. Procedure-specific risk -adjustment models including patient risk factors and hospital characteristics			
Risk of incomplete adjustment	**Low** Good adjustment with available data			

*used New York's Statewide Planning and Research Cooperative System - distinguishes comorbid conditions present at admission from complications.

Rosseel 2010	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	No	No	No	All cases in one MSF surgical unit
Data used				
Variables used				
Risk of imprecision				

(*Continued*)

Risk of imbalance	**High** certain major procedures such as caesarean section more likely to be supervised by PA than minor procedures such as wound debridement	**Unclear**	**Unclear**	**Low**
Analysis method	Bivariate analysis only			
Risk of incomplete adjustment	**High**			

Silber 2000a	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	Yes	Yes	No	Yes
Data used	Medicare Part A form	HCFA (Healthcare Financing Administration) database for stay of interest - codes in 3 months before admission Also MedisGroups severity scores on 73% of patients		American hospital annual surveys
Variable used	42 DRG (diagnosis-related group) procedure codes	27 patient characteristics		11 hospital characteristics Or 245 hospitals entered as separate strata in Mantel-Haenszel models
Risk of imprecision	**Low**	**High** Many conditions may be uncoded, for example smoking or obesity No details given on MedisGroups score		**Medium**
Risk of imbalance	**High** Undirected cases more likely to be emergency department admission	**High** Undirected more likely to be older, male and cardiac problems		**High** Hospitals with undirected cases smaller, less specialized technology and facilities, less teaching

(*Continued*)

Analysis method	Multivariate regression for each outcome. Final model contained variables which were significant at <0.05 in univariate model for any outcome and included 42 DRGs, 27 patient characteristics and 37 interaction terms Additional analyses used: multivariate models with MedisGroups scores 245 hospitals entered as separate strata in Mantel-Haenszel models Propensity scores for mortality risk
Risk of incomplete adjustment	**Low** Thorough adjustment using the available data

Simonson 2007	Case-mix	Co-morbidity	Type of anaesthetic	Hospital characteristics
Considered	Yes - all caesarean sections	Yes		Yes
Data used		CHARS (Comprehensive Hospital Abstract and Reporting System) database		Authors' survey of participating hospitals
Variables used		Age, primary payer, type of admission, source of admission, 18 other co-morbidity codes - mainly complications of labour or pregnancy plus obesity, hypertension and diabetes. Also other complications including maternal distress, shock, hypotension and cardiac arrest		Hospital bed size, teaching status, urban location
Risk of imprecision	**Low**	**Medium**		**High** Survey data - some retrospective
Risk of imbalance	**Low**	**High** CRNA cases younger and more urgent admissions. Variations between patient groups but no consistent pattern		**High** Large difference in urban/rural. Not reported for size/ teaching status
Analysis method	Hierarchical multivariate logistic model			

(*Continued*)

Risk of incomplete adjustment	**High** Not clear which variables, and whether only selected ones, were entered in analysis. Obesity/diabetes etc not included in final model. Other labour complications entered as covariate - these may be on causal pathway. Possibility of over-adjustment?

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Andrew F Smith (AF)

Co-ordinating the review: Sharon R Lewis (SRL), Amanda Nicholson (AN)

Undertaking manual searches: SRL and AN

Screening search results: SRL and AN

Organizing retrieval of papers: SRL

Screening retrieved papers against inclusion criteria: SRL and AN

Appraising quality of papers: SRL and AN

Abstracting data from papers: SRL, AN and Phil Alderson (PA)

Writing to authors of papers for additional information: SRL

Providing additional data about papers: SRL and AN

Obtaining and screening data on unpublished studies: SRL and AN

Data management for the review: SRL and AN

Entering data into Review Manager (RevMan 5.1): n/a

RevMan statistical data: n/a

Other statistical analysis not using RevMan: AN, PA

Interpretation of data: AN, PA, SRL and AS

Statistical inferences: AN, PA, AS, SRL

Writing the review: SRL, AN, AS

Securing funding for the review: AS

Performing previous work that was the foundation of the present study: AS

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: SRL

DECLARATIONS OF INTEREST

Sharon R Lewis: none

Phil Alderson: none

From March to August 2011, Amanda Nicholson worked for the Cardiff Research Consortium, which provides research and consultancy services to the pharmaceutical industry. The Cardiff Research Consortium has no connection with Amanda Nicholson's work with The Cochrane Collaboration. Amanda Nicholson's husband has small direct holdings in several drug and biotechnology companies as part of a wider balanced share portfolio.

Andrew F Smith was lead author on a previous non-Cochrane version of the review (Smith 2004). He was also funded by the UK Department of Health to run a project exploring the potential of employing non-medical anaesthetists in the UK healthcare setting (Kane 2005).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research Cochrane Collaboration Programme Grant. Enhancing the safety, quality and productivity of perioperative care. *Project Ref:* 10/4001/04., UK.

This grant funds the work of SL,AN & AS on this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had excluded obstetric patients from the protocol (Lewis 2013) but decided to include this important patient group within the review. Had their been sufficient and appropriate data to pool, we would have included the data for the obstetric patients separately.

Intervention and comparison group

We originally planned our second and third comparison groups to be:
2. an anaesthetic administered by a physician anaesthetist working as part of an anaesthetic team (e.g. team to include NPA, nurse anaesthetists, anaesthesia technicians etc.);
3. an anaesthetic administered by an NPA working as part of an anaesthetic team (e.g. team to include physician anaesthetist, nurse anaesthetists, anaesthesia technicians etc.).
We had planned to use the Medicare Advantage Medical Policy (Medicare Policy 2005) to distinguish between directed or supervised team work as it was anticipated that the majority of eligible studies would be based on Medicare data. For the purpose of billing, physician anaesthetists are required to define their work as personally performed, medically directed (performed by an NPA whilst the physician anaesthetist oversees no more than four concurrent procedures) or medically supervised (performed by an NPA who is directed by a physician other than the physician anaesthetist). The physician anaesthetist in the latter case may be responsible for overseeing more than four concurrent procedures. We had anticipated that the extent to which an NPA is working independently, that is without the medical direction of an anaesthetist, may be difficult to ascertain. During data extraction it was clear that it was not possible to separate these different groups and we decided to use a single comparison of NPA working under supervision or in a team.

Outcomes

We have modified the primary outcome 'serious airway complications' to 'anaesthesia-related complications' as we could not extract data separately on serious airways complications. We have modified the secondary outcome of other anaesthetic complications to 'other minor anaesthetic complications'.

We did not include any RCTs in the review as none were apparent during the search. We had specified methods for managing RCTs during the review process which are detailed below. If RCTs are carried out in the future, these following methods will be employed during an update.

Data extraction and management

The following items will be included in the RCT data extraction form.

- Methods: to include risk of bias assessments (see below).
- Patient group: to include age, sex, relevant sociodemographics, case-mix.
- Setting: e.g. rural or urban, country.
- Intervention: to include training, experience and the level of supervision, role and responsibilities of NPA.
- Comparison: to include training and experience of anaesthetist.
- Outcome: to include time points i. measured and ii. reported, unit of measurement.
- Results: to include missing participants, subgroup analyses.

Assessment of risk of bias in included studies

We will use the Cochrane risk of bias tool (Higgins 2011) for RCTs assessing the following.

i. Selection bias:

- sequence generation;
- allocation concealment.

ii. Performance bias:

- blinding of participants and personnel;
- blinding of outcome assessors.

iii. Attrition bias:

- incomplete outcome data;
- blinding of participants;
- personnel and outcome assessors.

iv. Detection bias:

- blinding of participants, personnel and outcome assessors;
- other potential threats to validity.

v. Reporting bias:

- selective outcome reporting.

Blinding of all personnel is clearly not feasible for this research question and blinding of participants may be difficult. It will be important to assess the comparability of intervention and comparison groups at baseline, examining the types of operation undertaken and co-morbidities and risk status of patients to exclude any selection bias.

We will record assessments as high risk, low risk or unclear and a risk of bias table will be completed for each eligible RCT. For each outcome, summary risk of bias assessments within domains will be presented in risk of bias graphs or figures and across domains in the 'summary of findings' table.

Measures of treatment effects for RCTs

For dichotomous outcomes, such as mortality, we will enter the total number of participants and number of events into RevMan (RevMan 5.1) to calculate risk ratios with 95% confidence intervals. For continuous data, such as length of hospital stay, we will calculate weighted mean differences. If data are presented in other forms and we are unable to source the original figures from the study authors, we may use the generic inverse variance option in RevMan. It is likely that patient reported satisfaction will be measured on different scales for each study. In this case we will use the standardized mean and mean differences when combining results. Cost of

different anaesthetic providers will be standardized to GBP in 2010 using the Cochrane CCEMG EPPI-Centre Cost Converter (v.1.2) and the standardized values used in the review (http://eppi.ioe.ac.uk/costconverstion/default.aspx).

Unit of analysis issues for RCTs

Cluster-randomized trials may be included in the review, where hospitals or surgical units have been randomized. Some studies may have further levels of clustering, for example surgical units within hospitals. We will extract data from these studies directly only if the analysis properly accounts for the cluster design using methods such as multi-level modelling or generalised estimating equations. If these adjustments are not made within the report we will undertake additional analyses by recalculating standard errors based on the design effect (Section 16.3.6) (Higgins 2011). The resulting effect estimates and their standard errors will be analysed using generic inverse variance methods in RevMan.

Assessment of heterogeneity for RCTs

We expect there will be considerable heterogeneity with any RCTs due to differences in:

- countries (US, UK, other developed world, developing world);
- training and supervision of NPAs;
- patient groups including age and co-morbidity;
- types of surgery undertaken.

As discussed in the 'Background' section, differences between countries are likely to be the most important source of heterogeneity. If we find sufficient studies we will initially combine studies for each outcome within a region. Some variables, such as NPA salary and training, will only be investigated within a region as comparisons, as for example the salary of an NPA in US and Africa may be misleading. We will only combine studies across different regions in one meta-analysis if study design and type of intervention or comparison are equivalent. We will examine this heterogeneity visually using forest plots, initially across all studies and then grouped by the factors which might explain the variation. Heterogeneity will be assessed using the Chi^2 and I^2 statistics and explored using subgroup analyses and meta-regression. The presence of an I^2 value of more than 80% would argue against presenting a pooled value.

Assessment of reporting biases for RCTs

We will aim to minimise reporting bias by identifying trials in progress or that are unreported from trial registers and contacting authors. If sufficient studies are included in the review we will review funnel plots to detect any publication bias and test for this statistically using Egger's test.

Reporting bias may also occur within studies, with certain outcomes not reported. By referring to the protocol, where available, we will identify outcomes which have been collected but not reported and contact authors to request data.

Data synthesis

We will attempt meta-analysis if we have two or more studies reporting comparable effect measures for a given outcome, and measures of heterogeneity are not excessive. An I^2 value of more than 80% would argue against presenting a pooled value. The choice of statistical model will depend on the studies that are included but we may need to use the inverse variance method for some outcomes.

Subgroup analysis and investigation of heterogeneity

We will analyse the subgroups described below for RCTs:

- countries - US, UK, other developed countries and developing countries;
- training and supervision of NPAs;
- patient group including age and co-morbidity; and
- type of surgery undertaken.

We will use differences in effect sizes, assessed by the I^2 statistic, between patient groups or types of procedures to address our subsidiary research question of whether NPAs might not be appropriate anaesthetic providers for certain patient groups.

Sensitivity analysis

For any data on patient reported outcomes we will undertake sensitivity analyses to assess whether unvalidated scales for outcomes such as pain or satisfaction affect results.

Summary of findings

We did not complete a summary of findings table as we did not combine data for this review.

Subgroup analysis and investigation of heterogeneity

We did not carry out subgroup analysis as we did not combine data for this review.

Sensitivity analysis

We did not carry out sensitivity analysis as we did not combine data for this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthesiology; *Nurse Anesthetists; *Physician Assistants; Anesthesia [adverse effects; mortality]; Anesthesia, Obstetrical [mortality]; Anesthetics [*administration & dosage; adverse effects]; Cesarean Section [mortality]; Cohort Studies; Observational Study as Topic; Retrospective Studies; Surgical Procedures, Operative [*statistics & numerical data]

MeSH check words

Female; Humans; Male