NCGC National Clinical Guideline Centre

Sedation in children and young people

Sedation for diagnostic and therapeutic procedures in children and young people

Appendices E to H

Royal College of Physicians
Royal College of Nursing
RCS ADVANCING SURGICAL STANDARDS
RCGP Royal College of General Practitioners
NHS Evidence accredited provider
NHS Evidence - provided by NICE www.evidence.nhs.uk

1 Appendix A - SCOPE

See separate file.

2 Appendix B - Declarations of interests

See separate file.

3 Appendix C – Search Strategies

See separate file.

4 Appendix D - Evidence tables

See separate file.

5 Appendix E- Meta-analyses forest plot

5.1 MIDAZOLAM

PLACEBO COMPARISONS

Oral Midazolam vs. placebo/no drug treatment

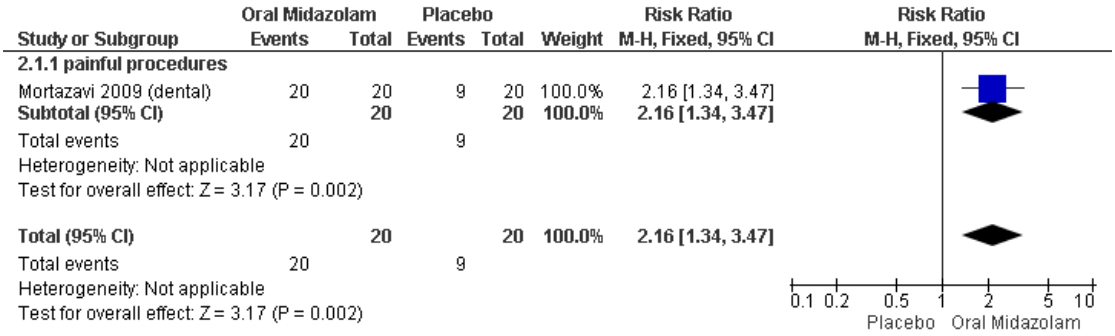

Figure 1 Mortazavi 2009: Completion of procedure [low quality evidence]

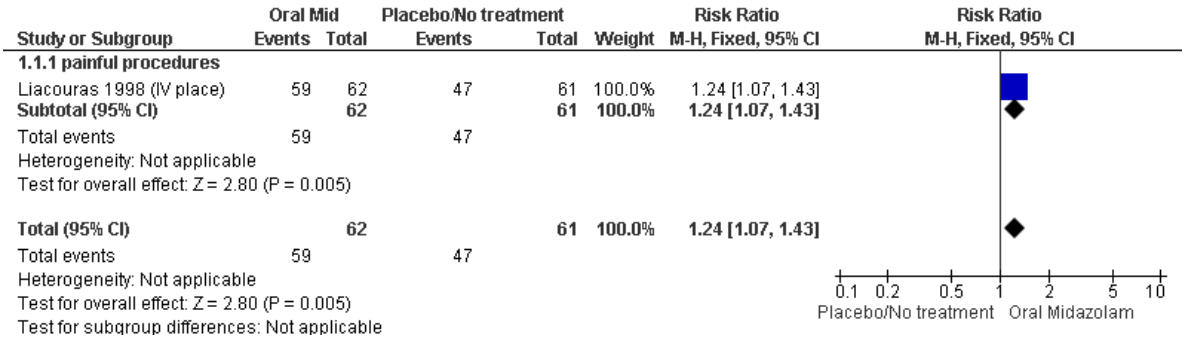

Figure 2 Liacouras 1998: Completion of procedure [moderate quality evidence]

Oral Midazolam + analgesia vs. placebo + analgesia

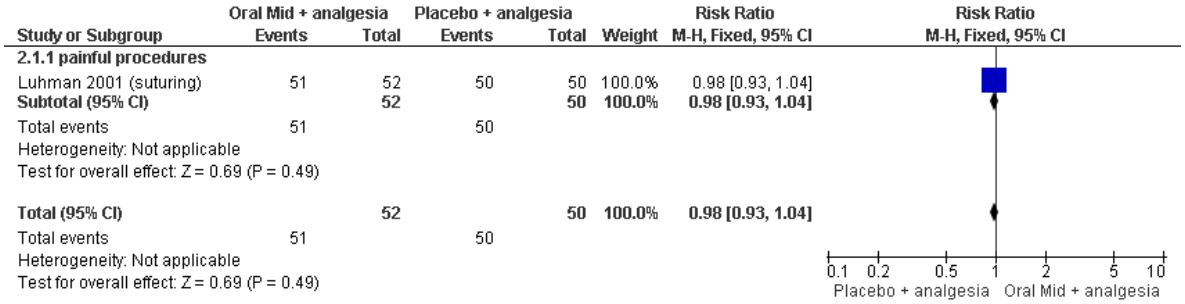

Figure 3 Luhman 2001: Completion of procedure [moderate quality evidence]

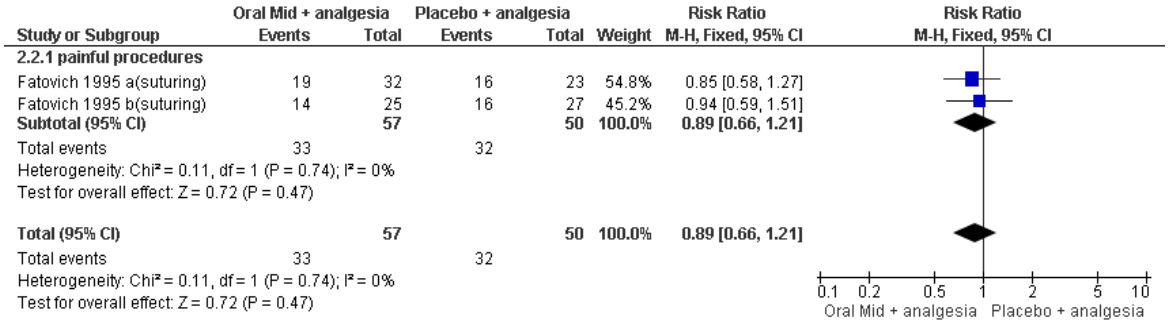

Figure 4 Fatovich 1995: Anxiety (no. of patients) assessed by observers using the Venham scale [moderate quality evidence]

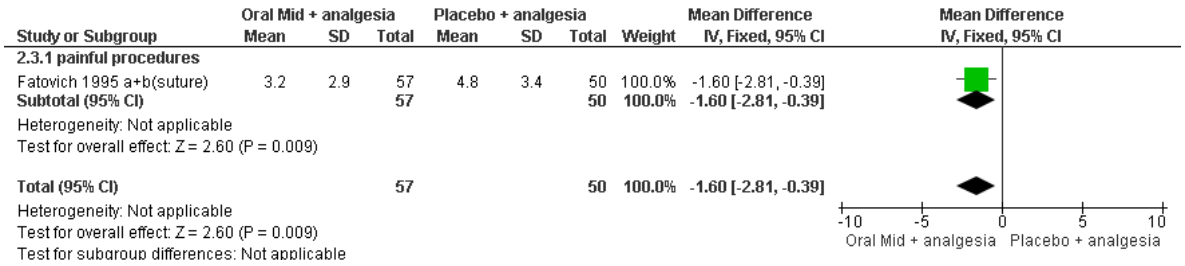

Figure 5 Fatovich 1995: Distress assessed by parents using the VAS scale [moderate quality evidence]

Oral Midazolam + non-pharmacological vs. placebo + non-pharmacological

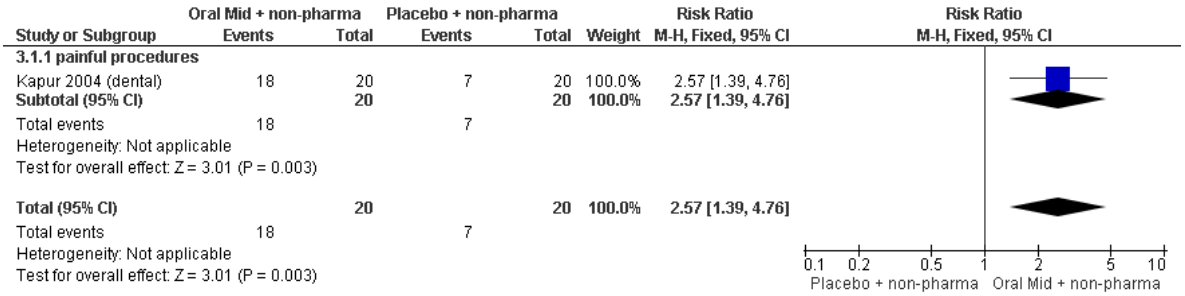

Figure 6 Kapur 2004: Completion of procedure [low quality evidence]

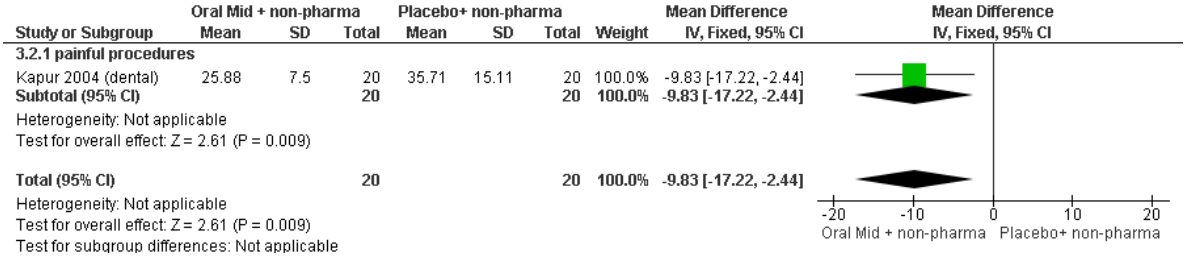

Figure 7 Kapur 2004: Duration of procedure [low quality evidence]

Intranasal midazolam vs. placebo

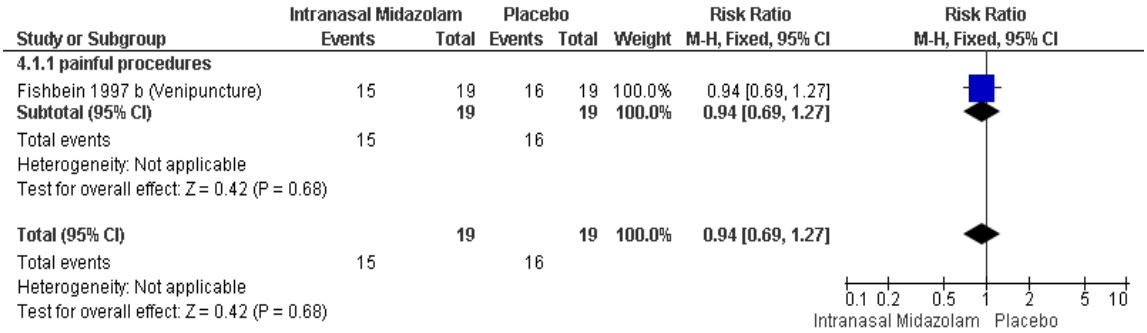

Figure 8 Fishbein 1997: Distress assessed by an observer using the OBRS scale [low quality evidence]

Intranasal midazolam + analgesia vs. placebo + analgesia

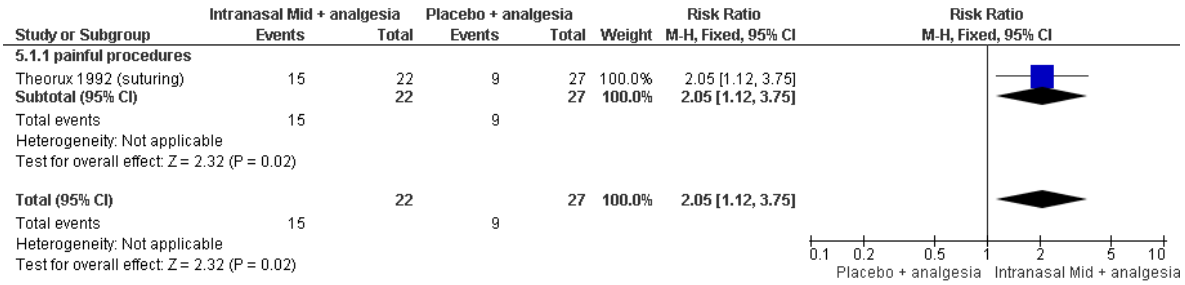

Figure 9 Theroux 1992: Parents' satisfaction (no. of patients) [low quality evidence]

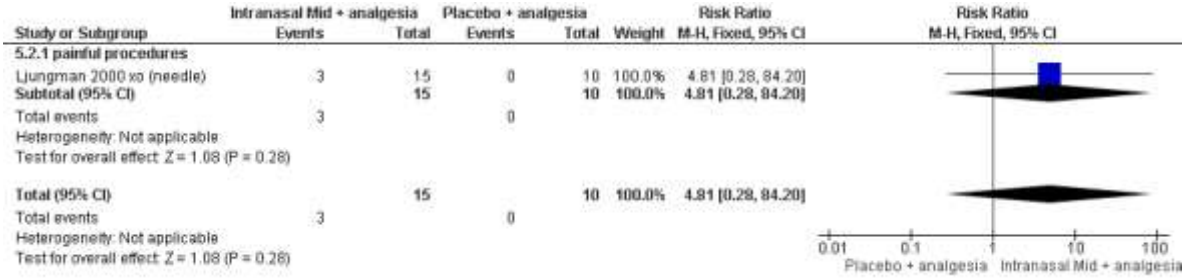

Figure 10 Ljungman 2000: Patients' preference (no. of patients) [very low quality evidence]

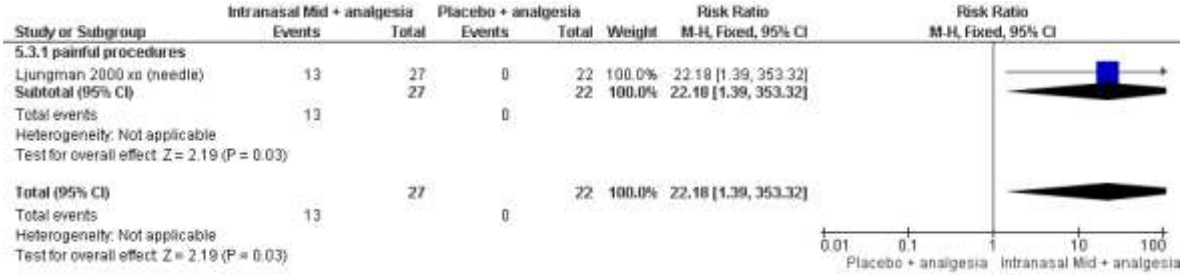

Figure 11 Ljungman 2000: Parents' preference (no. of patients) [low quality evidence]

HEAD to HEAD COMPARISONS

Oral midazolam vs. oral triclofos sodium

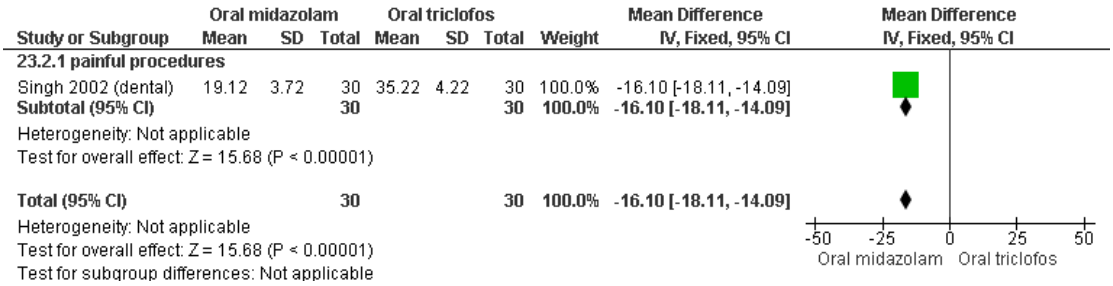

Figure 12 Singh 2002: Length of induction [low quality evidence]

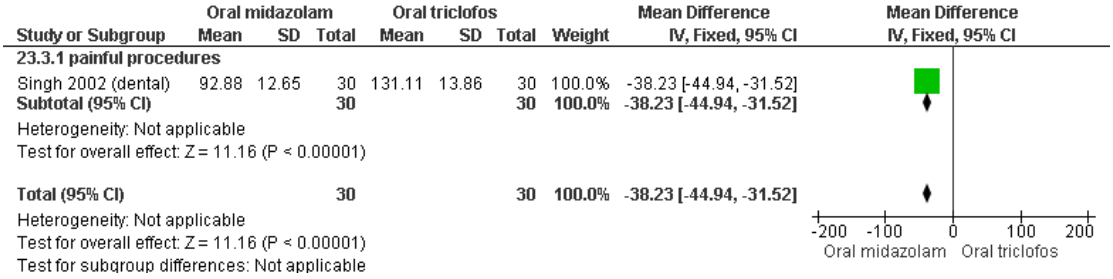

Figure 13 Singh 2002: Recovery tine [low quality evidence]

Sublingual midazolam vs. oral chloral hydrate

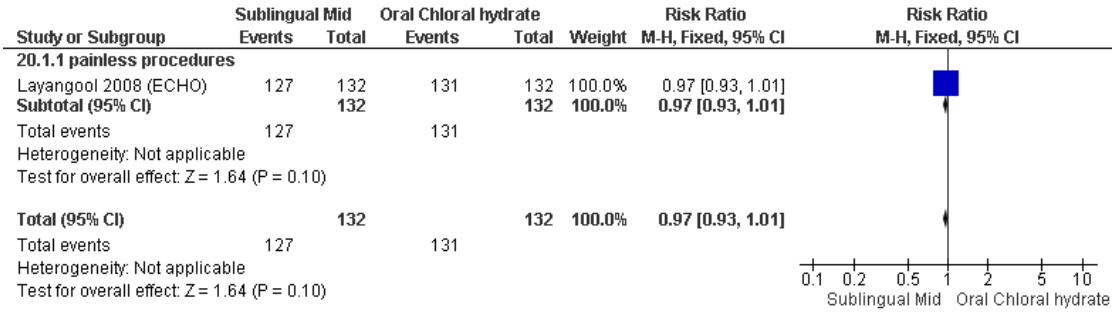

Figure 14 Layagool 2008: Completion of procedure [very low quality]

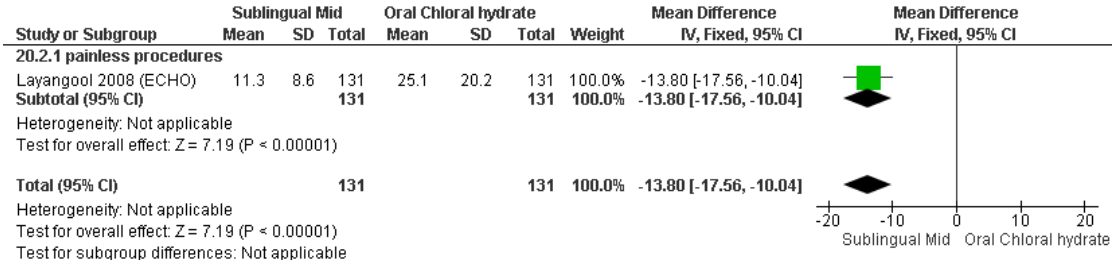

Figure 15 Layagool 2008: Induction time [low quality]

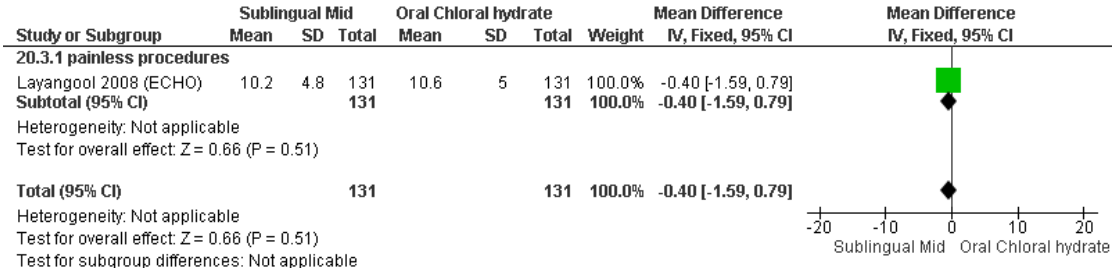

Figure 16 Layagool 2008: Duration of procedure [low quality]

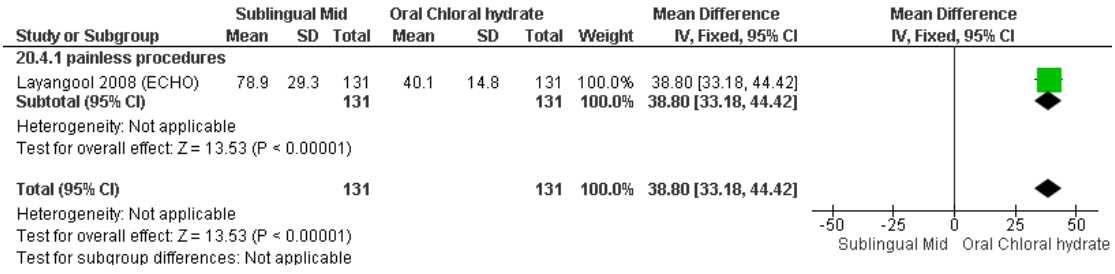

Figure 17 Layagool 2008: Total time [low quality]

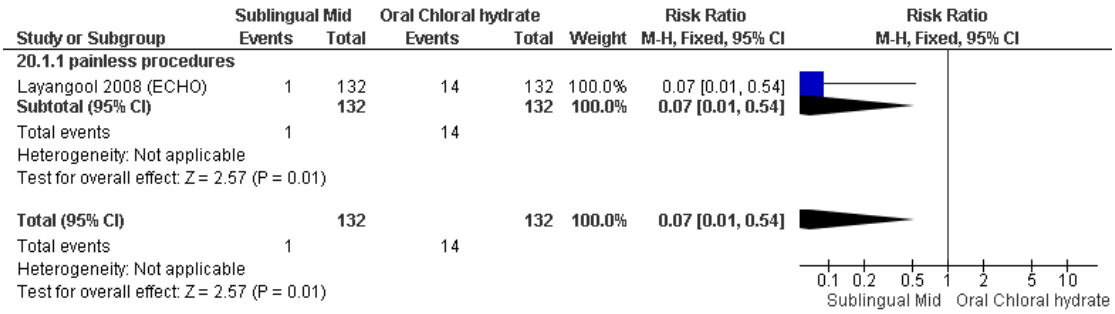

Figure 18 Layangool 2008: Vomiting [low quality evidence]

Rectal midazolam + placebo (for nitrous oxide) + topical anaesthesia + non-pharmacological intervention (distraction) vs. nitrous oxide (70%) + placebo (for midazolam) + topical anaesthesia + non-pharmacological intervention (distraction)

Figure 19 Zier 2008: Vomiting during drug nitrous oxide administration [moderate quality evidence]

COMBINATION COMPARISONS

Oral midazolam + topical anaesthesia + local anaesthesia vs. oral midazolam + nitrous oxide/oxygen + topical anaesthesia + local anaesthesia

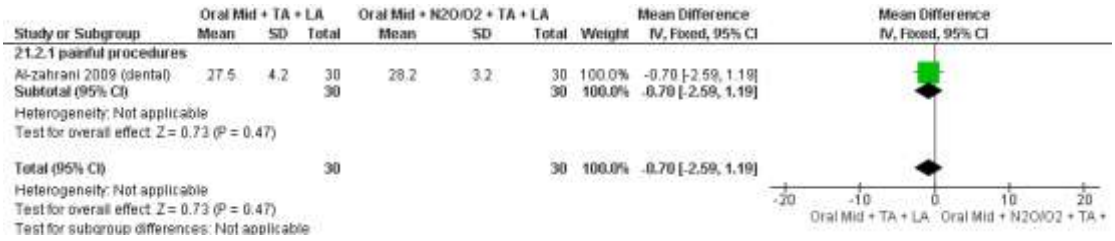

Figure 20 Al-zahrani 2009: Induction time [low quality evidence]

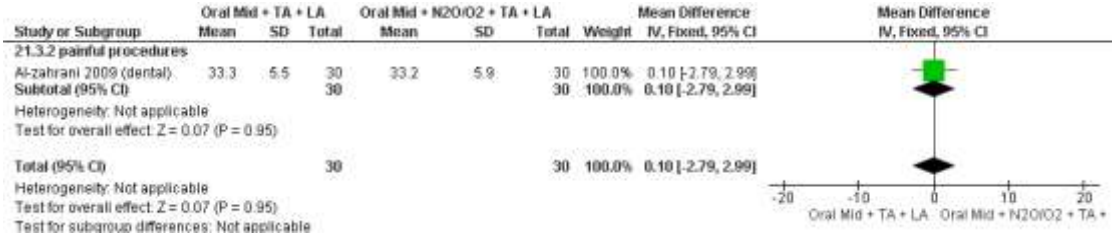

Figure 21 Al-zahrani 2009: Duration of procedure [low quality evidence]

Oral midazolam + nitrous oxide + analgesia vs. nitrous oxide + placebo + analgesia

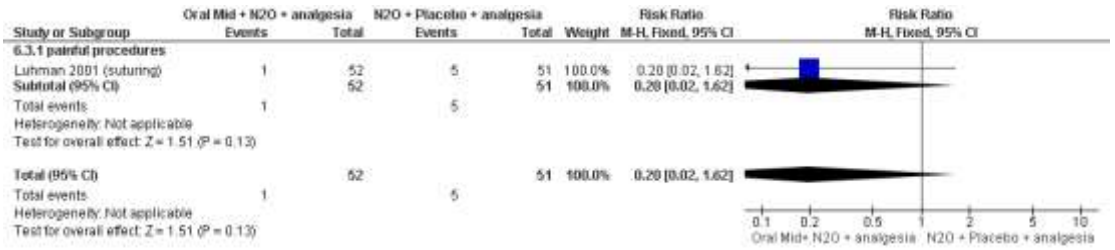

Figure 22 Luhman 2001: Vomiting [low quality evidence]

Oral midazolam + intravenous propofol + lidocaine vs. intravenous propofol + lidocaine

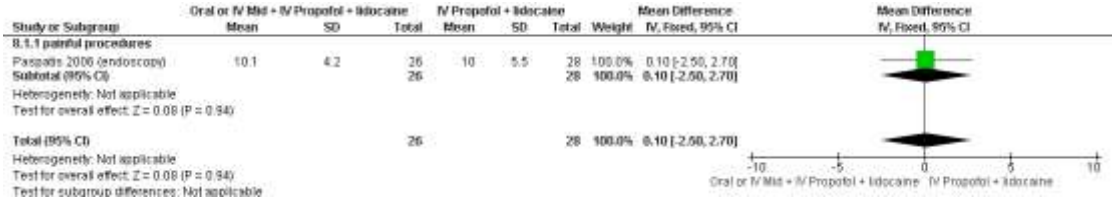

Figure 23 Paspatis 2006: Duration of procedure [low quality evidence]

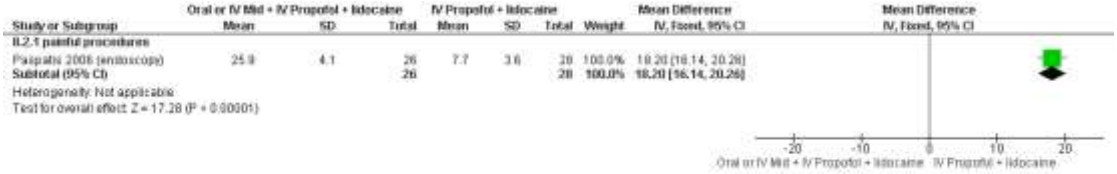

Figure 24 Paspatis 2006: Recovery time [moderate quality evidence]

Intravenous midazolam + intravenous meperidine vs. placebo + intravenous meperidine

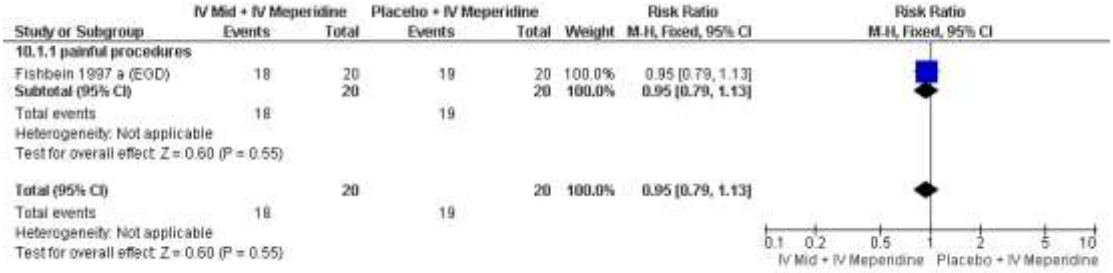

Figure 25 Fishbein 1997: Distress assessed by observer using OBRS [moderate quality evidence]

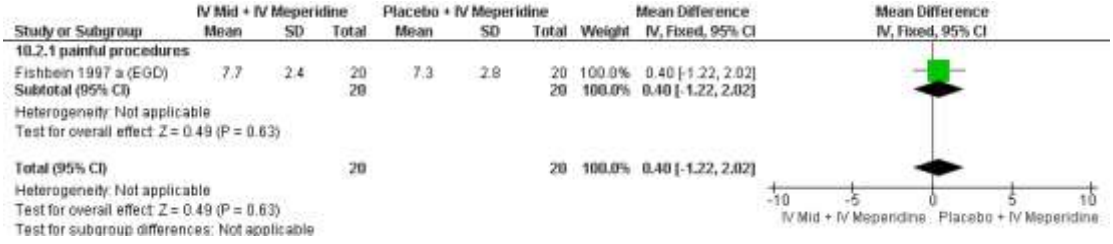

Figure 26 Fishbein 1997: Duration of procedure [low quality evidence]

Intravenous midazolam + intravenous propofol + lidocaine vs. intravenous propofol + lidocaine

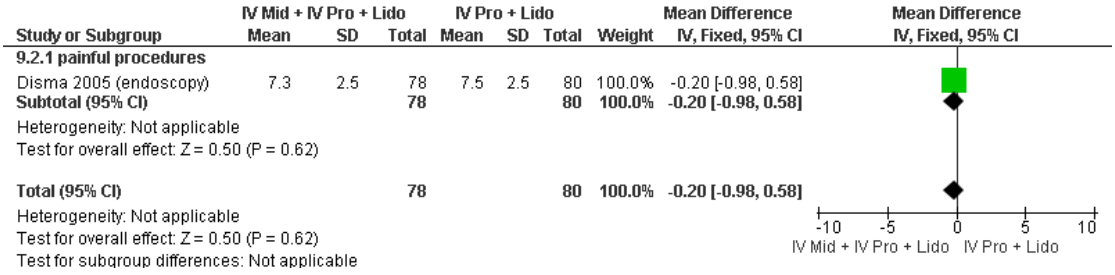

Figure 27 Disma 2005: Duration of procedure [moderate quality evidence]

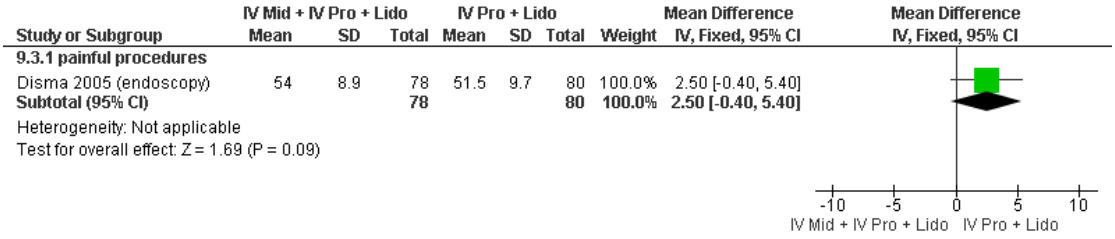

Figure 28 Disma 2005: Recovery time [low quality evidence]

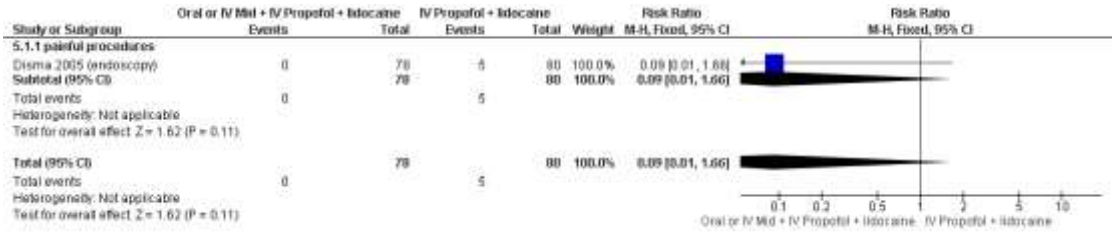

Figure 29 Disma 2005: Assisted ventilation (bag-valve mask) [low quality evidence]

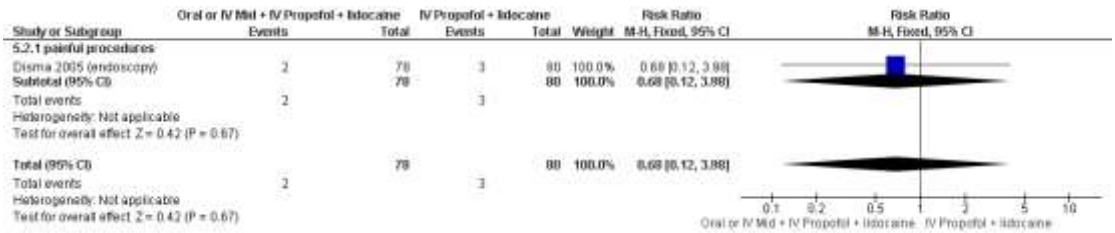

Figure 30 Disma 2005: Oxygen desaturation <90% [low quality evidence]

Intravenous midazolam + intravenous morphine + intravenous bolus-infusions placebo vs. Intravenous bolus infusion propofol + intravenous morphine + intravenous placebo + lidocaine

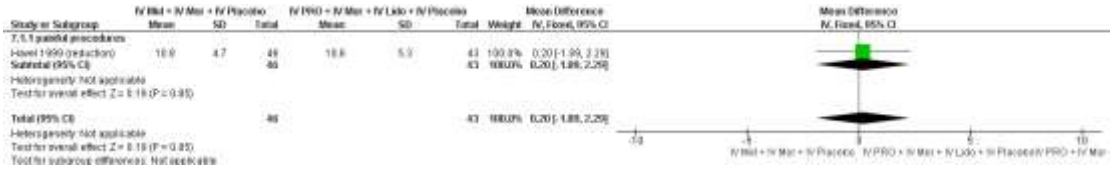

Figure 31 Havel 1999: Induction time [low quality evidence]

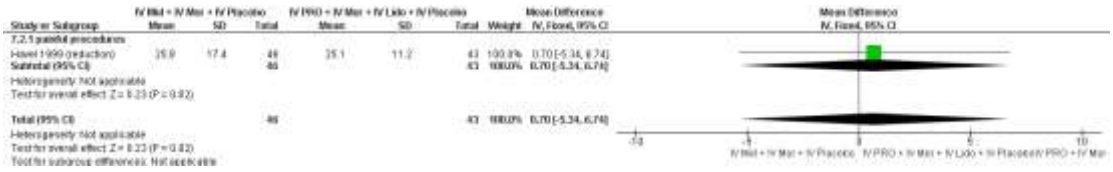

Figure 32 Havel 1999: Duration of procedure [low quality evidence]

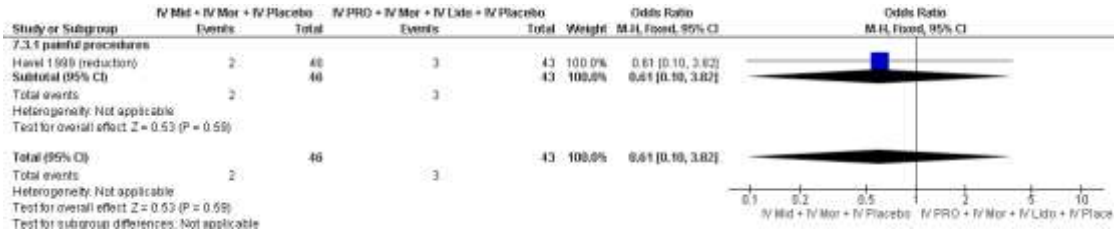

Figure 33 Havel 1999: Pain (no. of patients) [very low quality evidence]

Figure 34 Havel 1999: Recovery time [low quality evidence]

Figure 35 Havel 1999: Total time [low quality evidence]

Intravenous midazolam + intravenous fentanyl (analgesic) vs. intravenous fentanyl (analgesic)

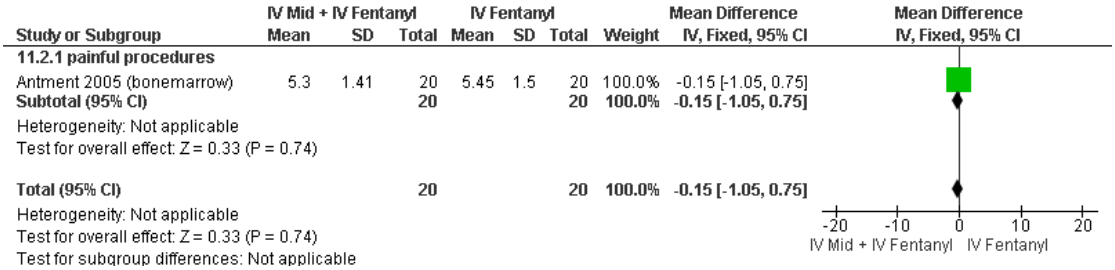

Figure 36 Antment 2005: Pain assessed by the anaesthetist using CHEOPS scale [very low quality evidence]

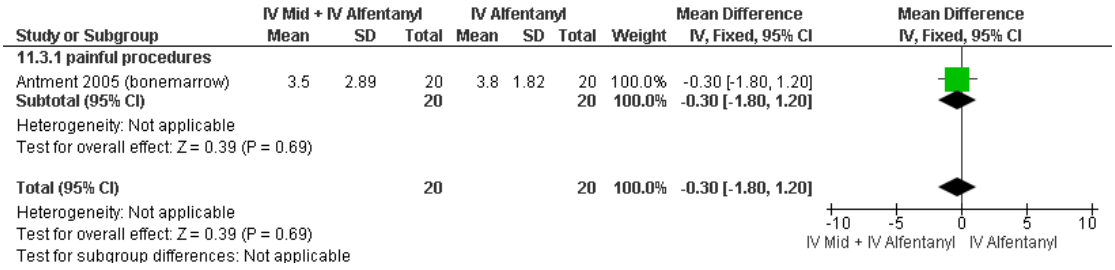

Figure 37 Antment 2005: Pain assessed by the anaesthetist using the VAS scale [very low quality evidence]

Intravenous midazolam + intravenous remifentanil (analgesic) vs. intravenous remifentanil (analgesic)

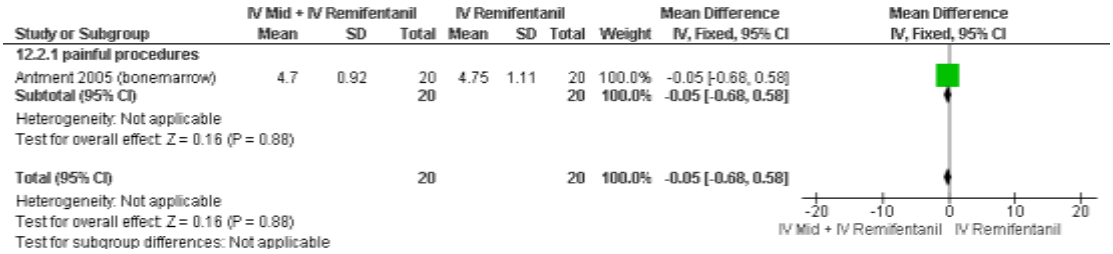

Figure 38 Antment 2005: Pain assessed by the anaesthetist using the CHEOPS scale [very low quality evidence]

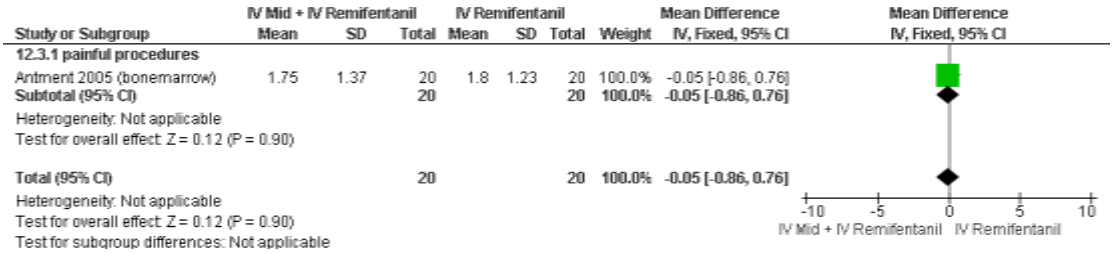

Figure 39 Antment 2005: Pain assessed by the anaesthetist using the VAS scale [very low quality evidence]

Intravenous midazolam + intravenous ketamine vs. intavenous ketamine + placebo

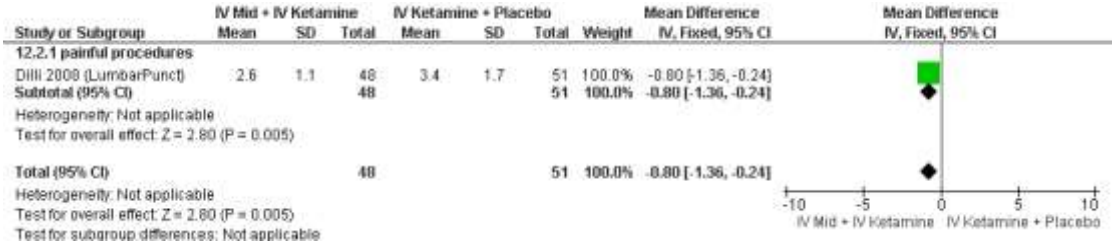

Figure 40 Dilli 2008: Induction time [very low quality evidence]

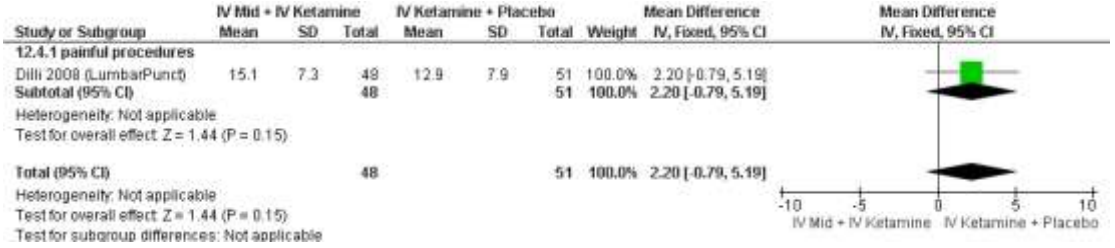

Figure 41 Dilli 2008: Recovery time [very low quality evidence]

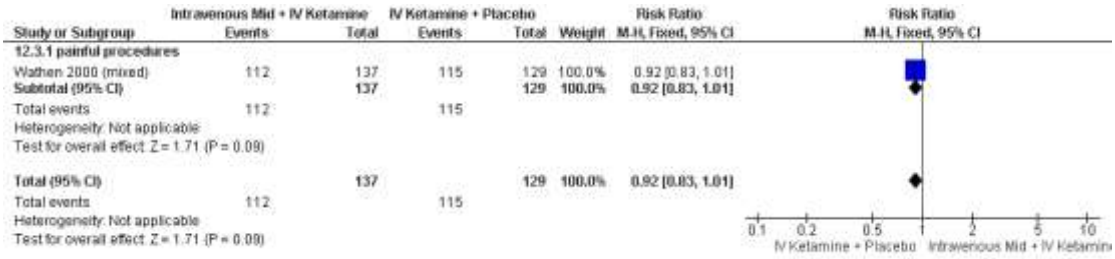

Figure 42 Wathen 2000: Parents' satisfaction [moderate quality evidence]

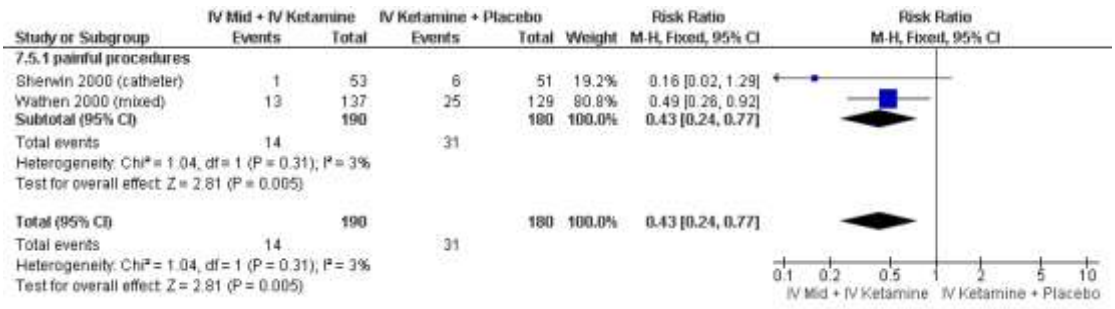

Figure 43 Sherwin 2000; Wathen 2000: Vomiting (during visit and at home 12 hrs after discharge and well into recovery) [low quality evidence]

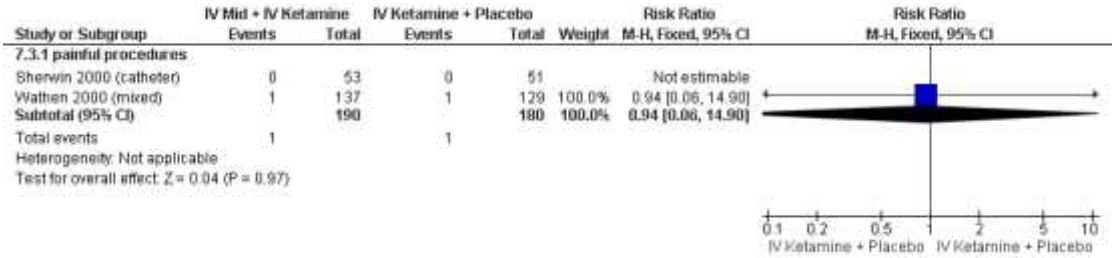

Figure 44 Sherwin 2000; Wathen 2000: Assisted ventilation (bag mask) [low quality evidence]

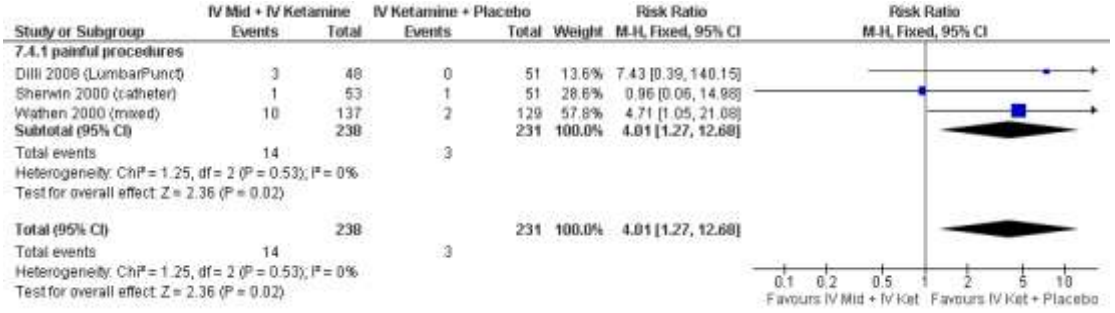

Figure 45 Sherwin 2000; Wathen 2000; Dilli 2008: Oxygen desaturation <90% [low quality evidence]

ROUTE OF ADMINISTRATION

Oral midazolam vs. intranasal midazolam

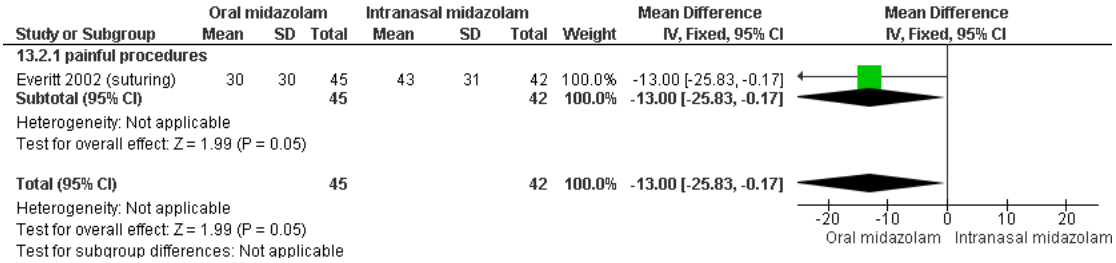

Figure 46 Everitt 2002: Distress assessed by observer using the VAS scale [very low quality evidence]

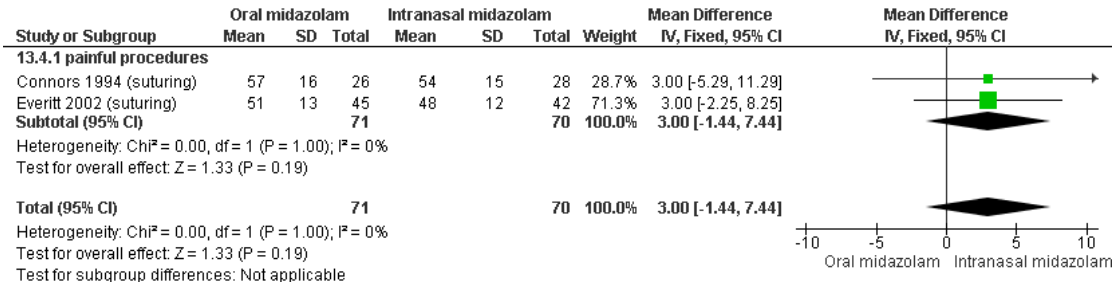

Figure 47 Connors 1994; Evertitt 2002: Total time [very low quality evidence]

Oral midazolam + nitrous oxide (40/45%) + lidocaine vs. intranasal midazolam + nitrous oxide (40/45%) + lidocaine

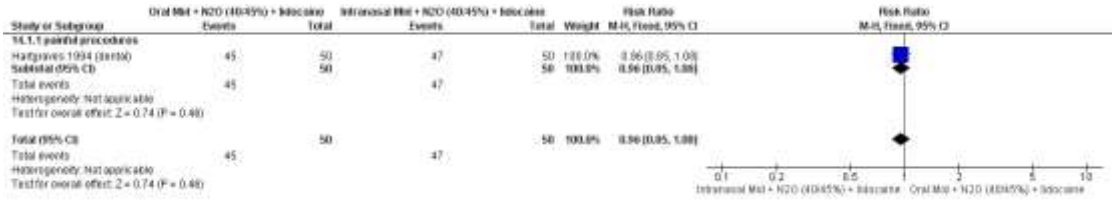

Figure 48 Hartgraves 1994: Completion of procedure [low quality evidence]

Figure 49 Lee-Kim 2004: Induction time [moderate quality evidence]

Figure 50 Lee-Kim 2004: Total time [low quality evidence]

Oral Midazolam + nitrous oxide (40/45%) + lidocaine vs. Intranasal Midazolam + nitrous oxide (40/45%) + lidocaine

Figure 51 Hartgraves 1994: Oxygen desaturation < 90% [very low quality evidence]

Intranasal midazolam + analgesia vs. intramuscular midazolam+ analgesia

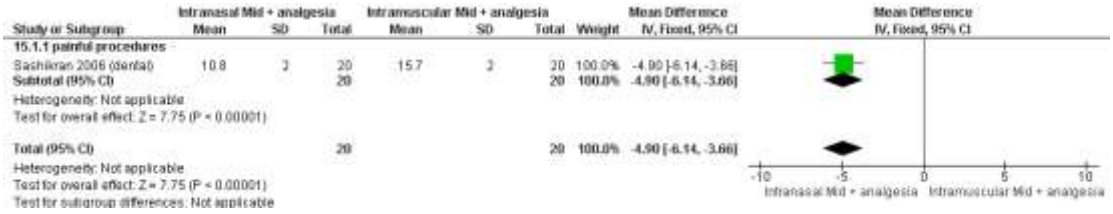

Figure 52 Sashikran 2006: Induction time [moderate quality evidence]

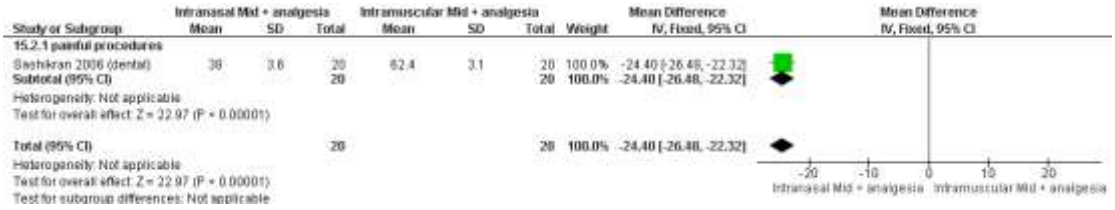

Figure 53 Sashikran 2006: Recovery time [moderate quality evidence]

DOSE COMPARISONS

Intranasal midazolam 0.3mg/kg + nitrous oxide vs. intranasal midazolam 0.2 mg/kg + nitrous oxide

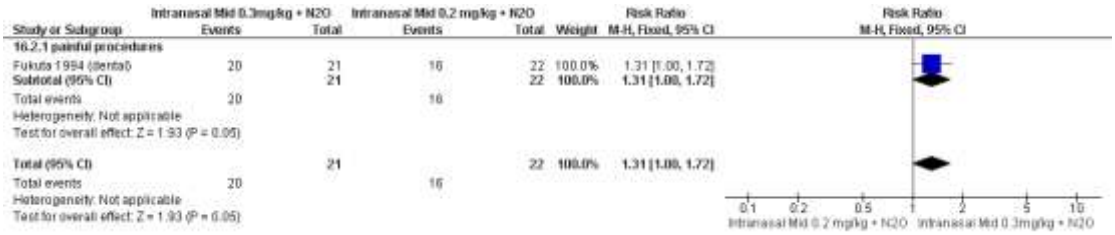

Figure 54 Fukuta 1994: Completion of procedure [low quality evidence]

Figure 55 Fukuta 1994: Duration of procedure [low quality evidence]

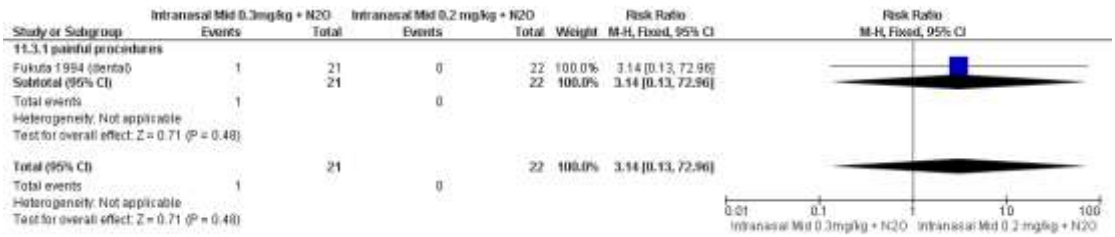

Figure 56 Fukuta 1994: Oxygen desaturation <90% [very low quality evidence]

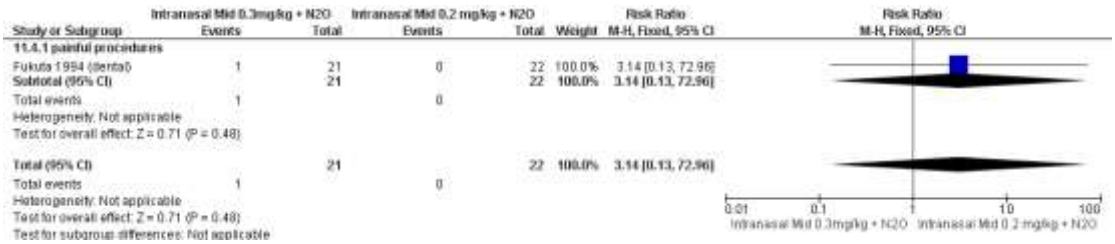

Figure 57 Fukuta 1994: Vomiting [very low quality evidence]

Rectal midazolam 2mg/kg + lidocaine vs. rectal midazolam 1mg/kg + lidocaine

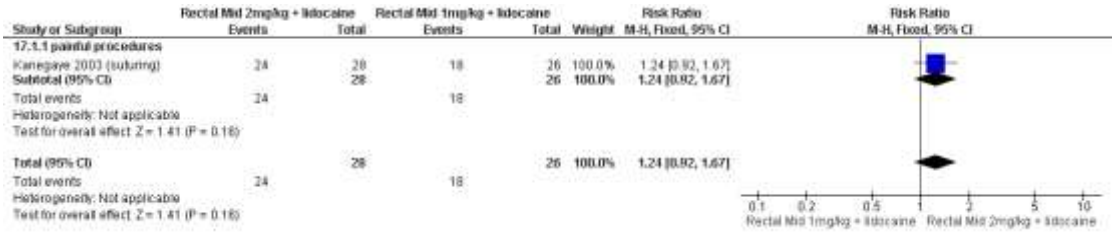

Figure 58 Kanegaye 2003: Parents' satisfaction [low quality evidence]

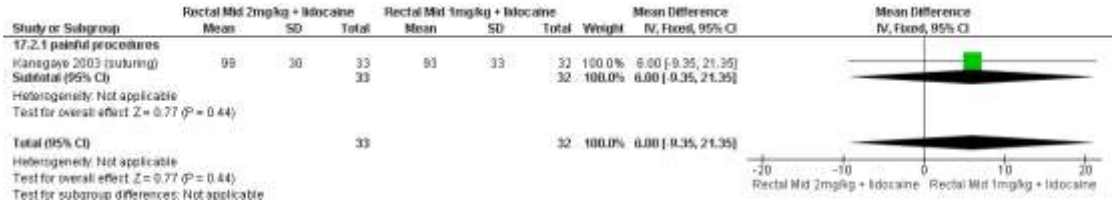

Figure 59 Kanegaye 2003: Total time [low quality evidence]

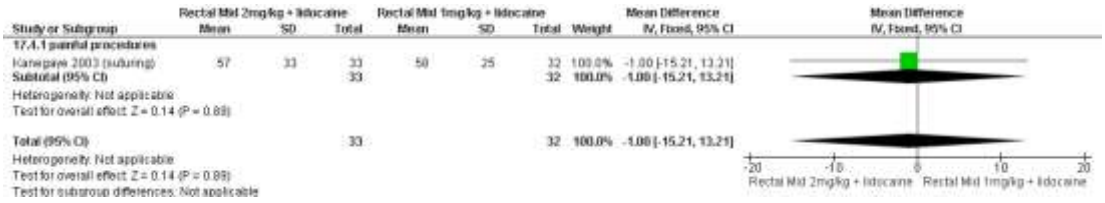

Figure 60 Kanegaye 2003: Recovery time [low quality evidence]

5.2 TRICLOFOS SODIUM

HEAD to HEAD COMPARISON

Oral triclofos sodium vs. oral midazolam

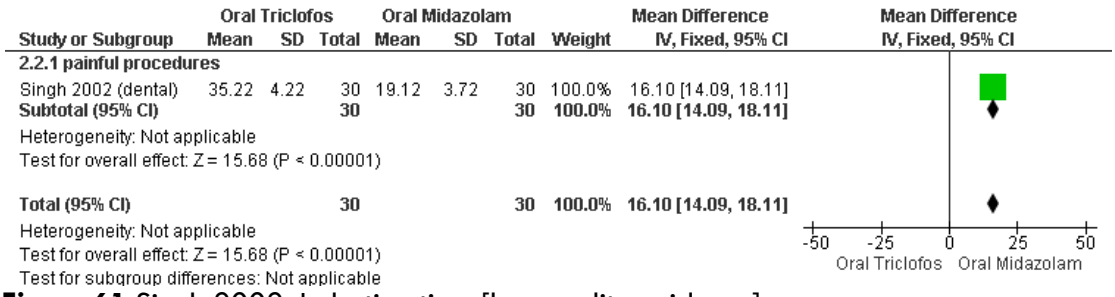

Figure 61 Singh 2002: Induction time [low quality evidence]

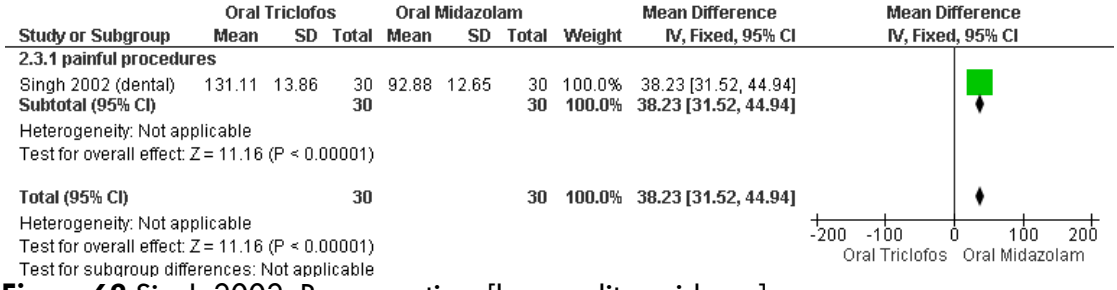

Figure 62 Singh 2002: Recovery time [low quality evidence]

5.3 NITROUS OXIDE

Nitrous oxide vs. behavioural management

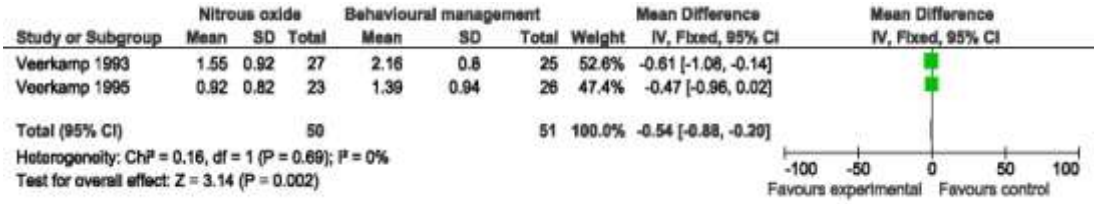

Figure 63 Veerkamp 1993; Veerkamp 1995: Anxiety assessed using the Venham scale [very low quality evidence]

Nitrous oxide vs. oral midazolam

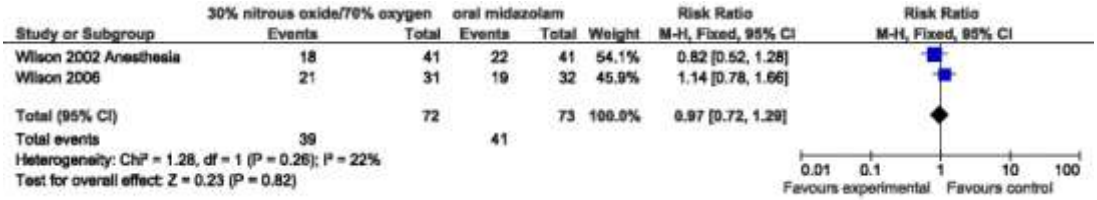

Figure 64 Wilson 2002; Wilson 2006: Patients' preference [moderate quality evidence]

5.4 SEVOFLURANE

COMBINATION COMPARISONS

Sevoflurane + nitrous oxide + intravenous midazolam vs. medical air + intravenous midazolam

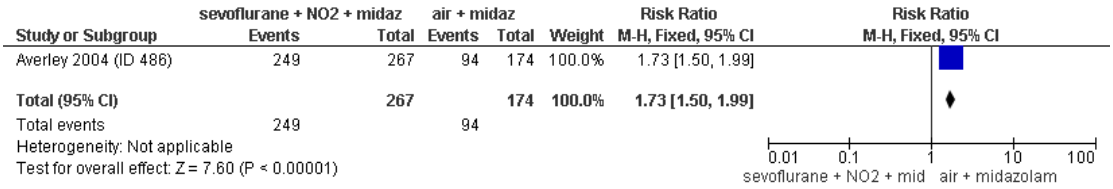

Figure 65 Averley 2004: Completion of procedure [High quality evidence]

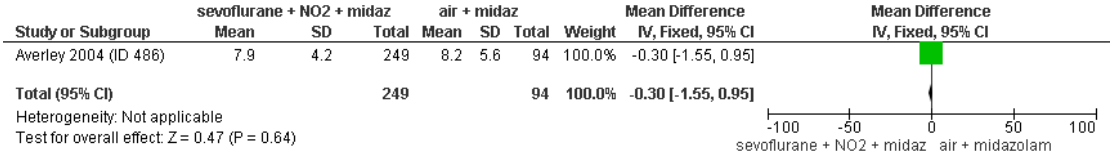

Figure 66 Averley 2004: Recovery time [moderate quality evidence]

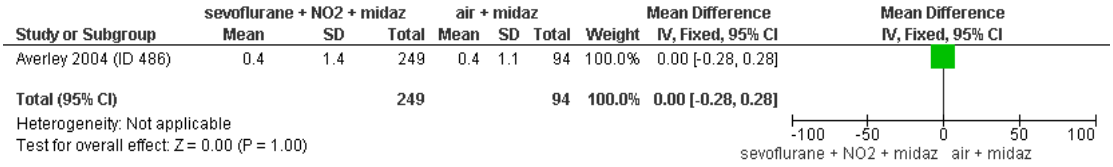

Figure 67 Averley 2004: Pain assessed by children using VAS [moderate quality evidence]

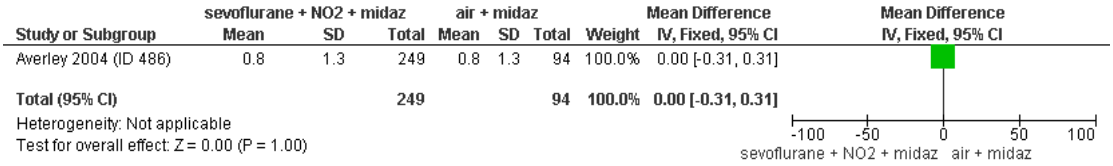

Figure 68 Averley 2004: Anxiety assessed by children using VAS [moderate quality evidence]

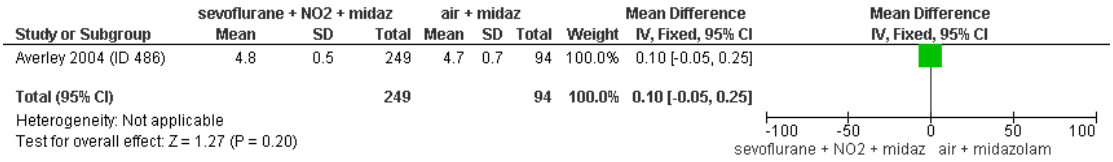

Figure 69 Averley 2004: Parents' satisfaction [moderate quality evidence]

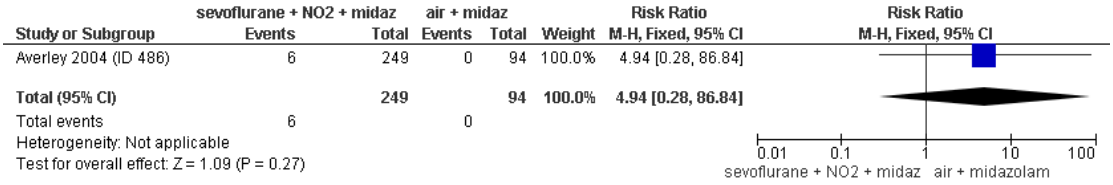

Figure 70 Averley 2004: Vomiting [very low quality evidence]

Sevoflurane + nitrous oxide + intravenous midazolam vs. nitrous oxide + intravenous midazolam

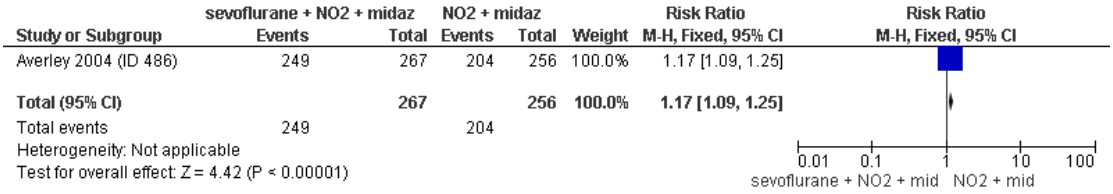

Figure 71 Averley 2004: Completion of procedure [High quality evidence]

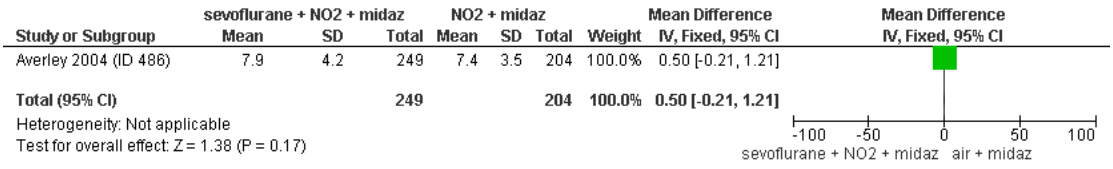

Figure 72 Averley 2004: Recovery time [moderate quality evidence]

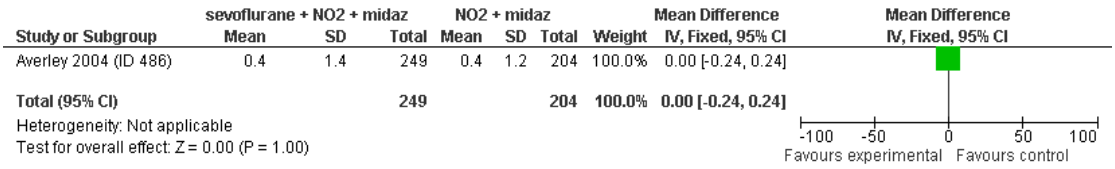

Figure 73 Averley 2004: Pain assessed by children using VAS [moderate quality evidence]

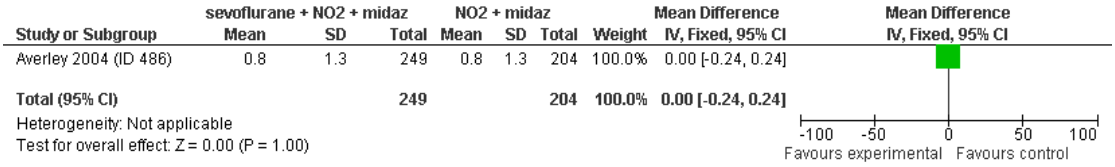

Figure 74 Averley 2004: Anxiety assessed by children using VAS [moderate quality evidence]

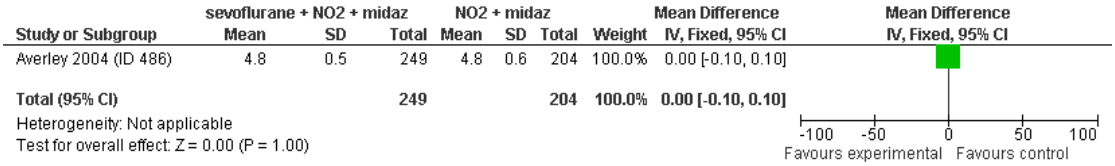

Figure 75 Averley 2004: Parents' satisfaction [moderate quality evidence]

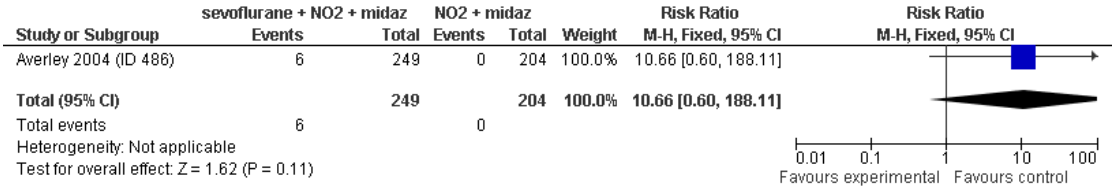

Figure 76 Averley 2004: Vomiting [very low quality evidence]

Sevoflurane + nitrous oxide vs. nitrous oxide

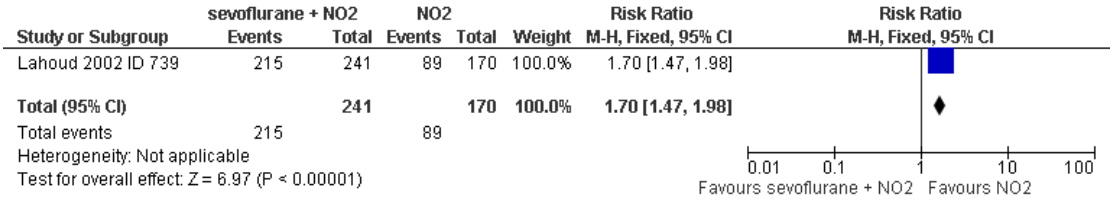

Figure 77 Lahoud 2002: Completion of procedure [moderate quality evidence]

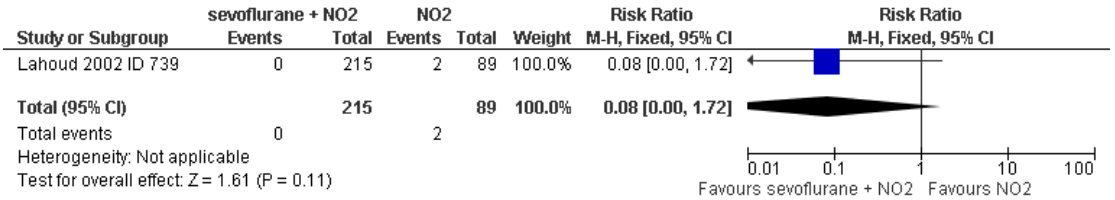

Figure 78 Lahoud 2002: Anxiety (no. of patients) assessed using the Venham scale [very low quality evidence]

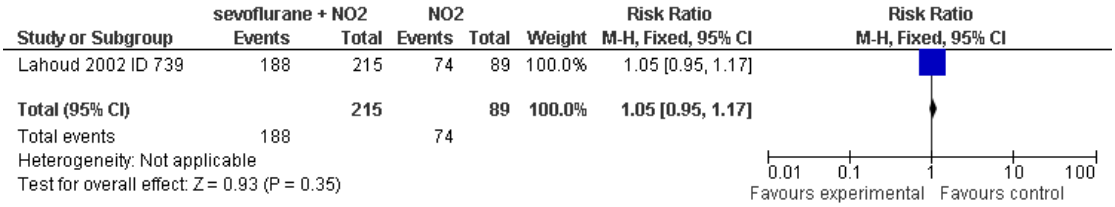

Figure 79 Lahoud 2002: Patients' satisfaction (no. of patients) [low quality evidence]

5.5 PROPOFOL

COMBINATION COMPARISONS

Intravenous propofol + propofol maintenance + local anaesthesia vs. intravenous midazolam + intravenous ketamine + intravenous fentanyl

Figure 80 Vardi 2002: Duration of procedure [low quality evidence]

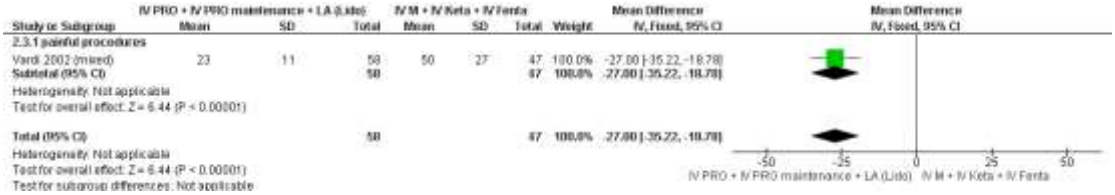

Figure 81 Vardi 2002: Recovery time [low quality evidence]

Figure 82 Vardi 2002: Satisfaction at induction period assessed by four observers using the Ramsay scale [very low quality evidence]

Figure 83 **Vardi 2002: Satisfaction scores at sedation period assessed by four observers using the Ramsay scale [very low quality evidence]**

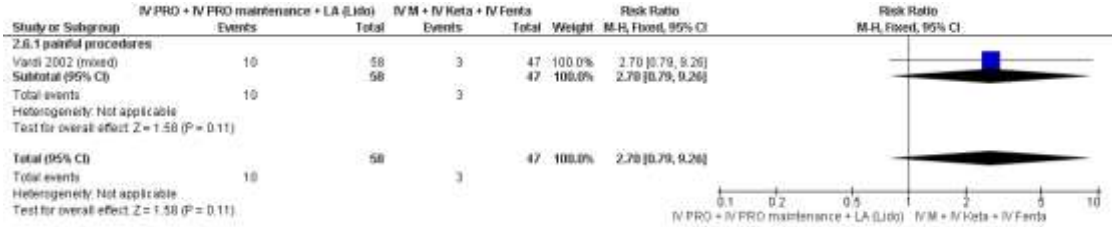

Figure 84 Vardi 2002: Assisted ventilation (bag mask) [very low quality evidence]

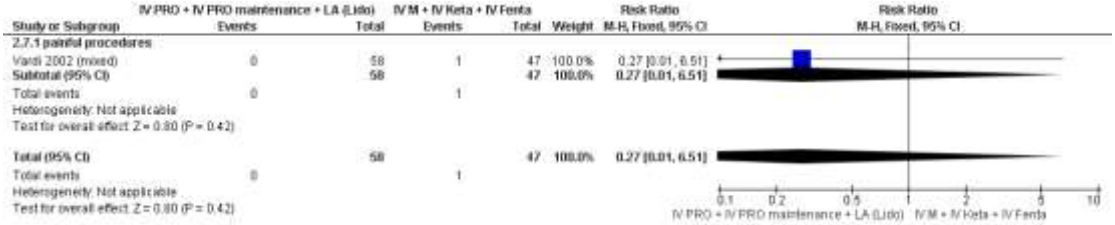

Figure 85 Vardi 2002: Endotracheal intubation [very low quality evidence]

5.6 OPIOIDS

COMBINATION COMPARISONS

Intravenous fentanyl + intravenous propofol versus intravenous propofol + placebo

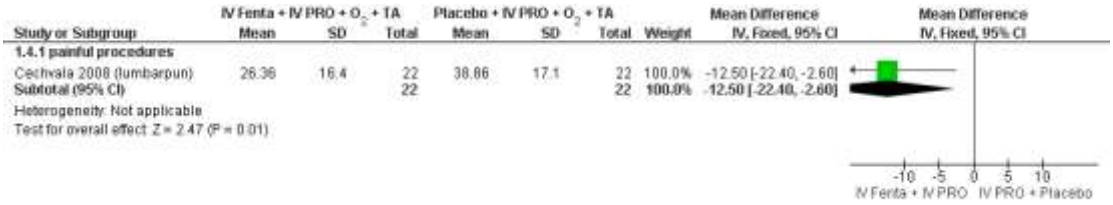

Figure 86 Cechvala 2008; Hollman 2008: Recovery time [moderate quality evidence]

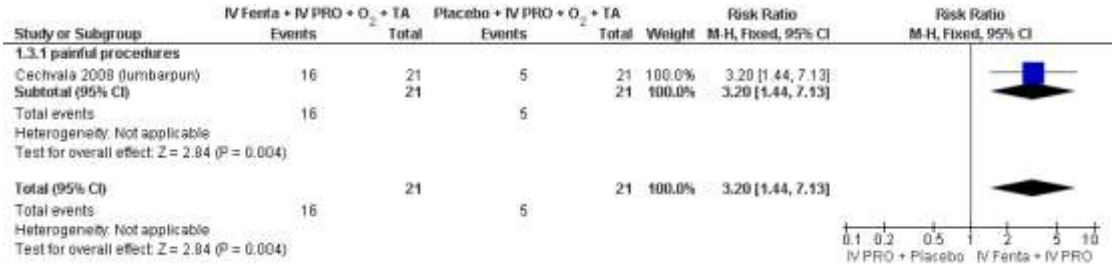

Figure 87 Cechvala 2008; Hollman 2008: Parents' preference [moderate quality evidence]

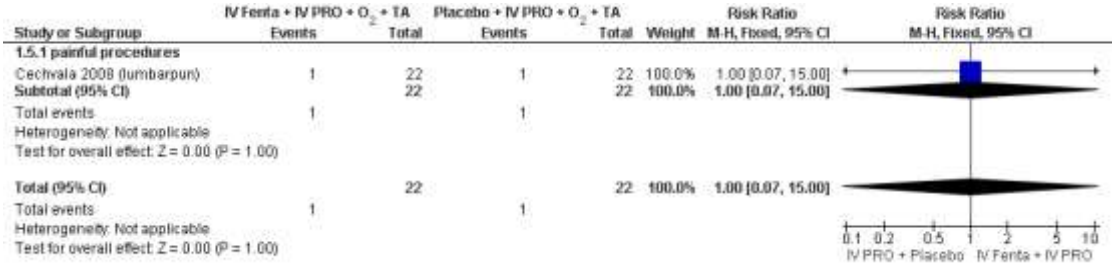

Figure 88 Cechvala 2008; Hollman 2008: Assisted ventilation (assisted ventilation by flow inflating anaesthesia bag) [low quality evidence]

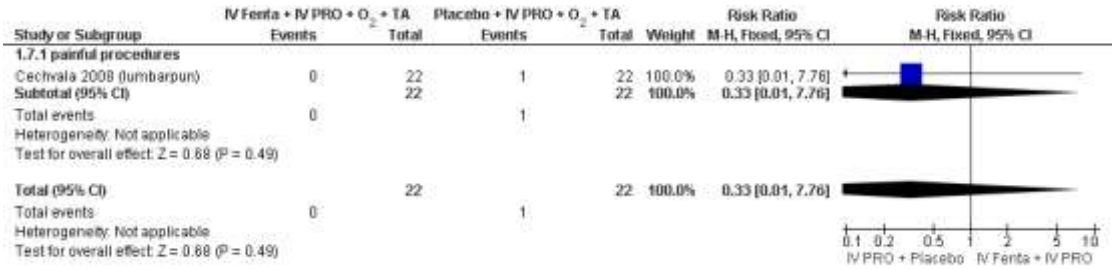

Figure 89 Cechvala 2008; Hollman 2008: Oxygen desaturation [low quality evidence]

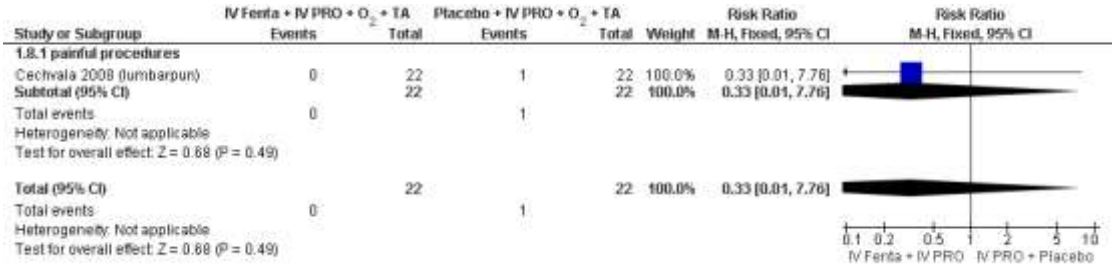

Figure 90 Cechvala 2008; Hollman 2008: Vomiting [low quality evidence]

Intravenous fentanyl + intravenous propofol + topical anaesthesia versus intravenous propofol + topical anaesthesia

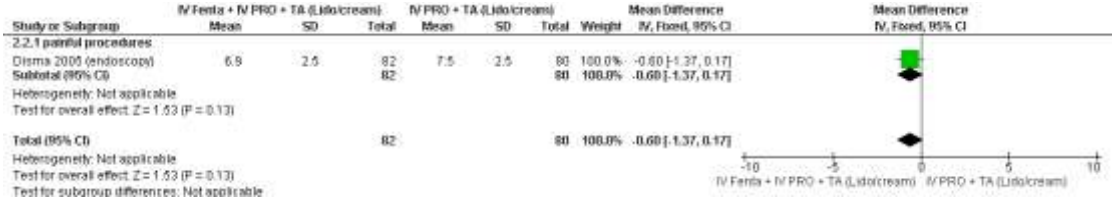

Figure 91 Disma 2005: Duration of procedure [low quality evidence]

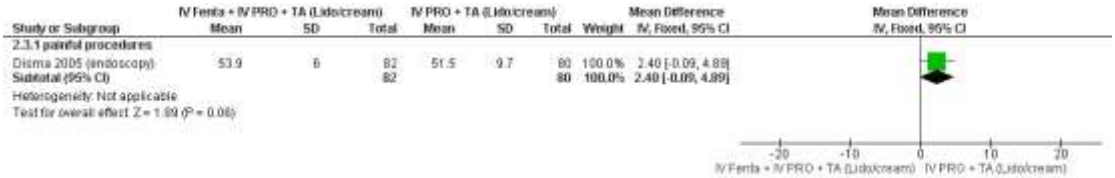

Figure 92 Disma 2005: Recovery time (Aldrete score ≥ 8) [low quality evidence]

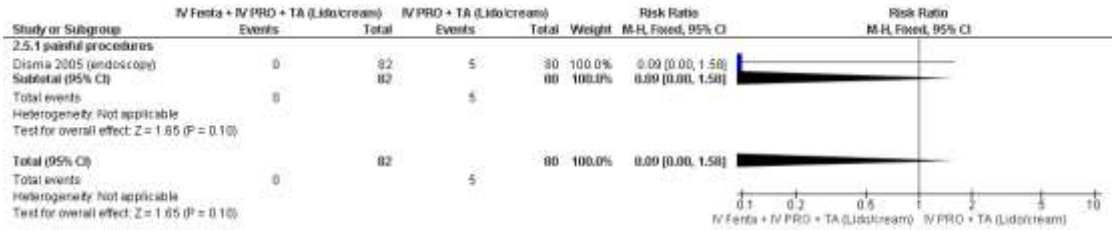

Figure 93 Disma 2005: Assisted ventilation (bag mask) [low quality evidence]

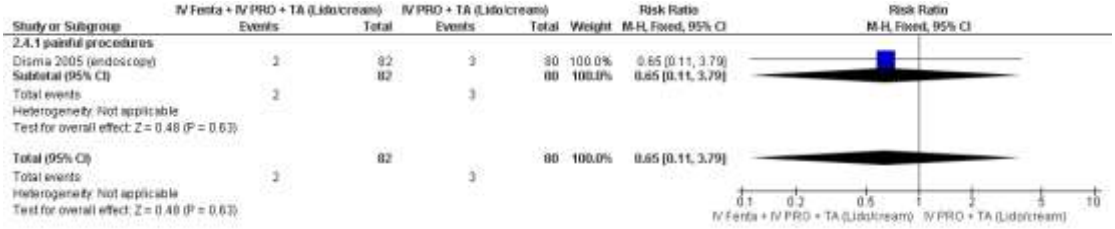

Figure 94 Disma 2005: Oxygen desaturation <90% [low quality evidence]

Intravenous fentanyl + intravenous propofol + topical anaesthesia versus intravenous midazolam + intravenous propofol + topical anaesthesia

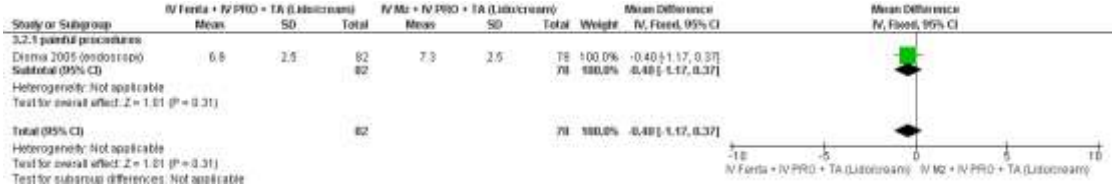

Figure 95 Disma 2005: Duration of procedure [moderate quality evidence]

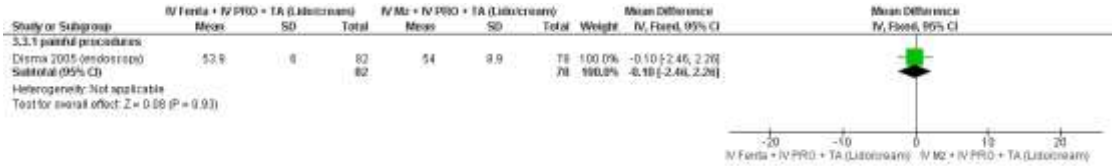

Figure 96 Disma 2005: Recovery time (Aldrete score ≥ 8) [moderate quality evidence]

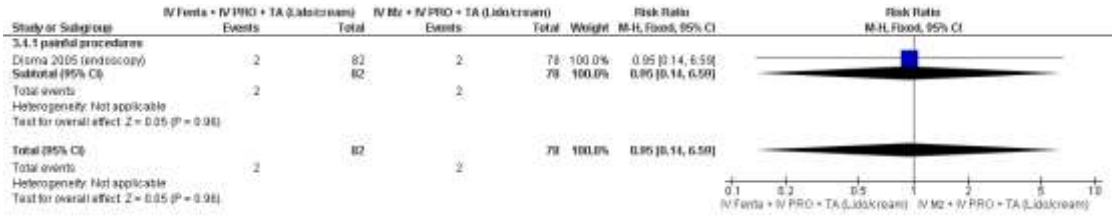

Figure 97 Disma 2005: Oxygen desaturation <90% [very low quality evidence]

Intravenous fentanyl + intravenous midazolam vs. intravenous midazolam + intravenous ketamine

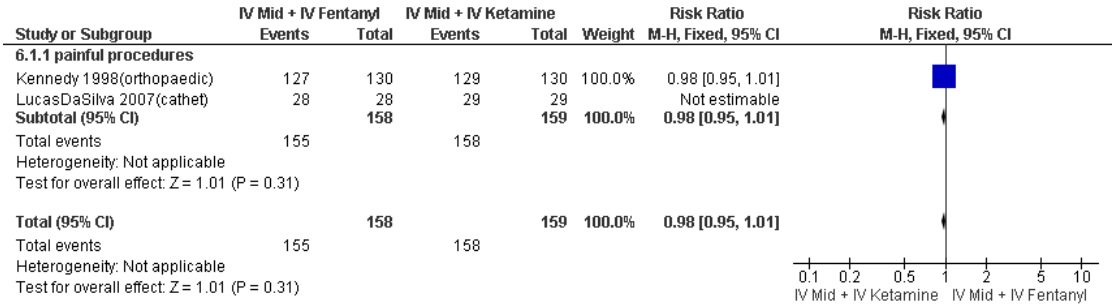

Figure 98 LucasDaSilva 2007; Kennedy 1998: Completion of procedure [low quality evidence]

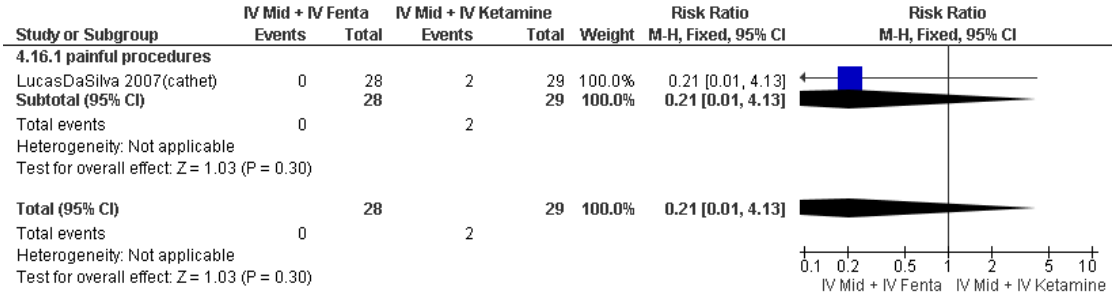

Figure 99 LucasDaSilva 2007: Oxygen desaturation <90% [low quality evidence]

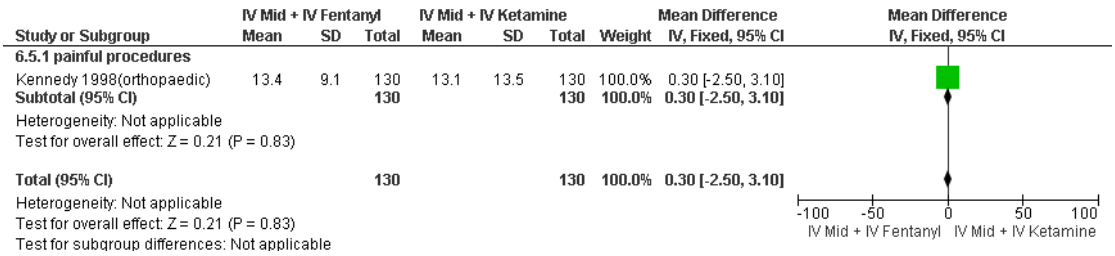

Figure 100 Kennedy 1998: Induction time [low quality evidence]

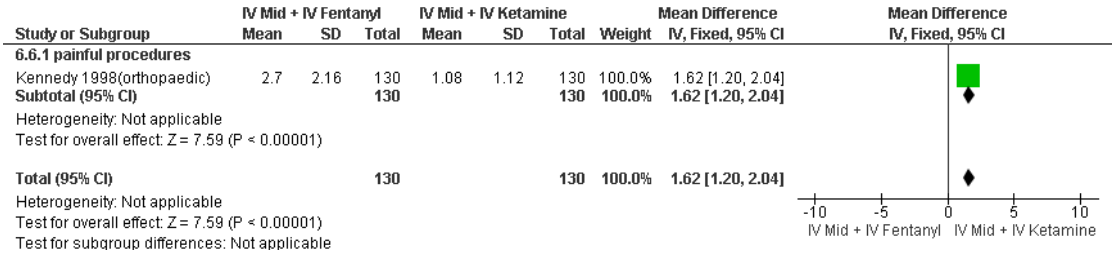

Figure 101 Kennedy 1998: Distress assessed by observer using the OBSDR scale [low quality evidence]

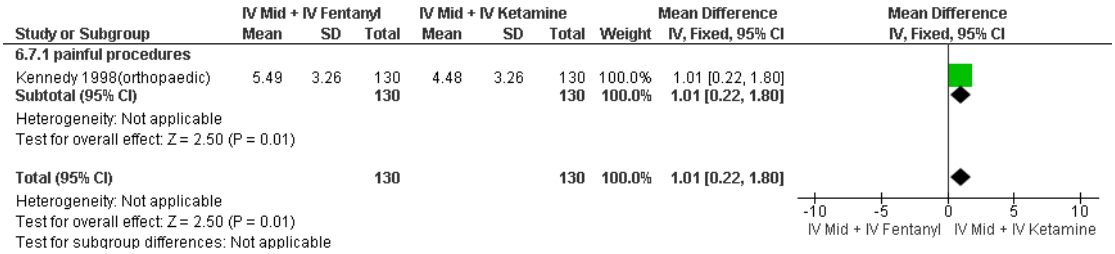

Figure 102 Kennedy 1998: Anxiety assessed by parent using the VAS scale [low quality evidence]

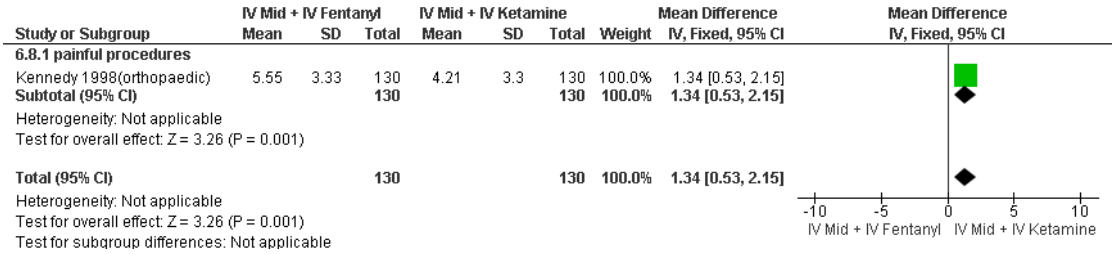

Figure 103 Kennedy 1998: Pain during procedure assessed by parent using the VAS scale [low quality evidence]

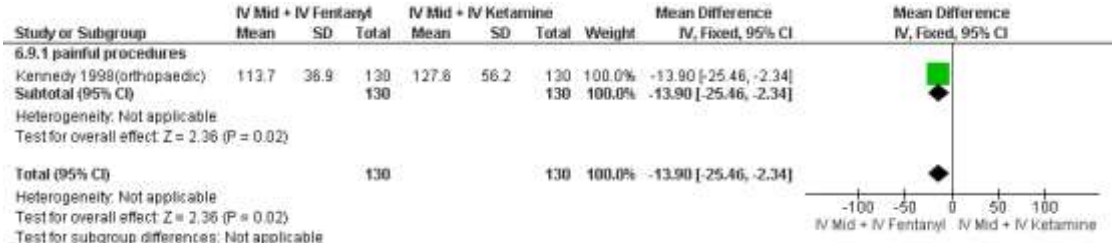

Figure 104 Kennedy 1998: Total time [low quality evidence]

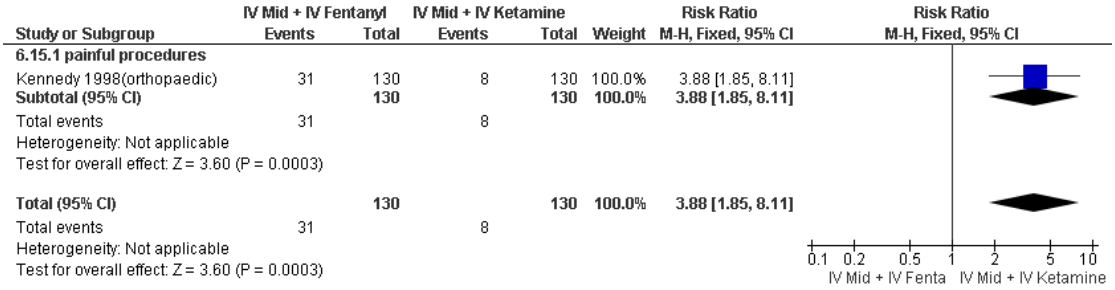

Figure 105 Kennedy 1998: Oxygen desaturation <90% [low quality evidence]

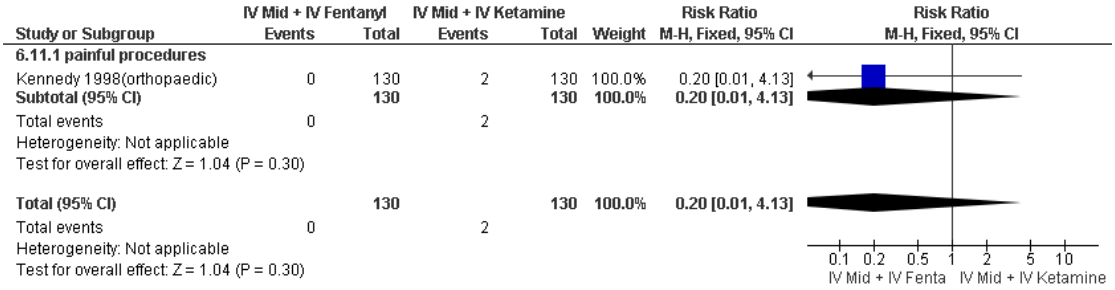

Figure 106 Kennedy 1998: Assisted ventilation (bag mask) [low quality evidence]

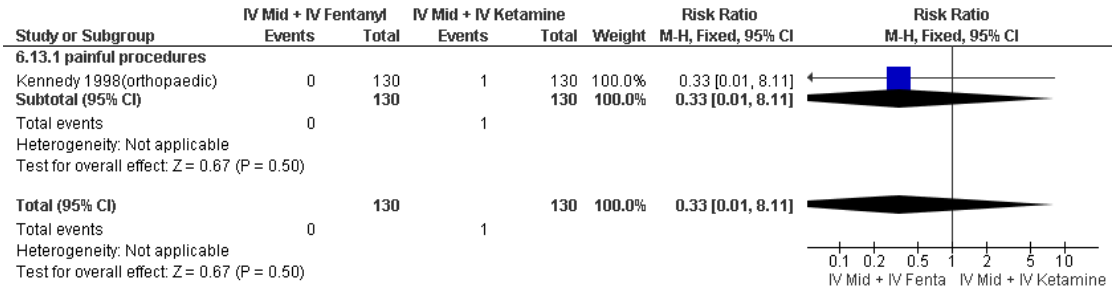

Figure 107 Kennedy 1998: Vomiting during procedure [low quality evidence]

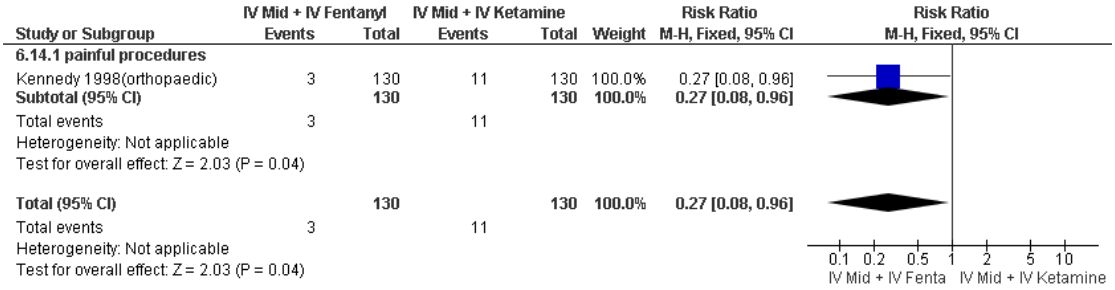

Figure 108 Kennedy 1998: Vomiting during recovery [low quality evidence]

Intravenous fentanyl + intravenous propofol + topical anaesthesia versus intravenous propofol + intravenous ketamine + topical anaesthesia

Figure 109 Tosun 2007: Duration of procedure [moderate quality evidence]

Figure 110 Tosun 2007: Pain (no. of patients) during induction [low quality evidence]

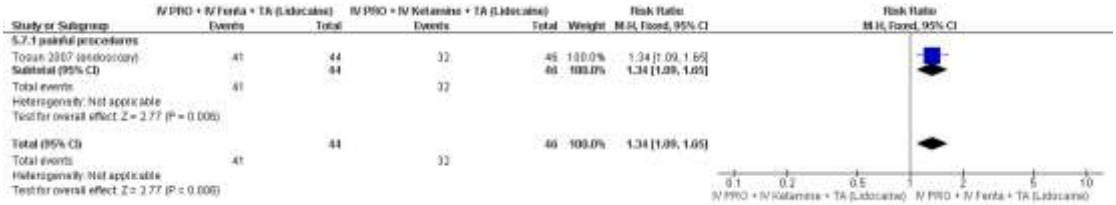

Figure 111 Tosun 2007: Pain (no. of patients) during procedure [low quality evidence]

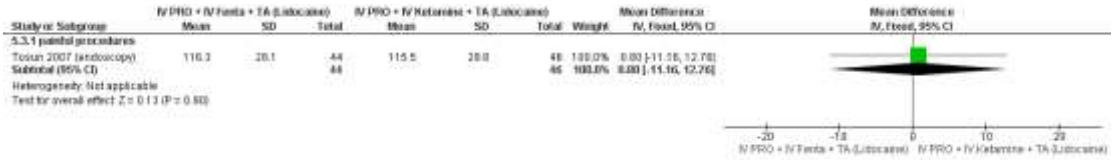

Figure 112 Tosun 2007: Recovery time [low quality evidence]

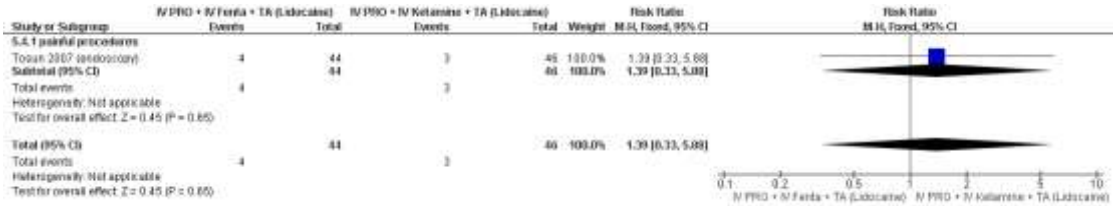

Figure 113 Tosun 2007: Oxygen desaturation <90% [low quality evidence]

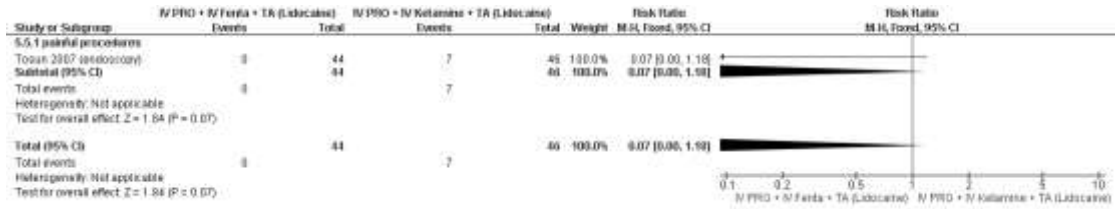

Figure 114 Tosun 2007: Vomiting [low quality evidence]

6 Appendix F - Cost-effectiveness analysis

6.1 Introduction

Appropriate sedation techniques should have the potential to prevent the need to abandon and reschedule procedures when sedation is unsuccessful. This will minimise distress, discomfort for and risk of harm to patients as well as reduce QALY loss due to long term morbidity or mortality. Additionally, it will reduce the use of the National Health Services (NHS).

We have conducted a search of existing economic evaluations that could reliably inform the guideline recommendations. We identified five studies[19,20,26,33,39] but all had potentially serious limitations (see 6.9 and 6.10 below). We therefore developed a *de novo* economic evaluation to determine the cost-effectiveness of different techniques. The model was constructed to determine the most appropriate sedation technique.

Population

The clinical effectiveness and safety review suggests that different sedation techniques are suitable for different population groups (see chapter 6 on clinical effectiveness of sedation techniques). We developed models for the following common procedures:

- Dental procedures:
    - tooth extraction in children
    - tooth extraction in adolescents
- Short painful procedures: manipulation of forearm fracture
- Painless imaging: CT scan
- Endoscopy:
    - Oesophago-gastroscopy
    - Colonoscopy

A description of these groups is given in section 6.12, 'Further evidence to recommendations: clinical interpretation of evidence by setting'.

Interventions

The techniques are those for which the evidence suggests are clinically effective and safe (see chapter 6 on clinical effectiveness of sedation techniques). The GDG wanted the techniques on the list to capture the majority of techniques routinely used in the NHS. They advised that the techniques in the six population groups below should be evaluated in the model. In each group, the sedative techniques should be compared to general anaesthesia as this is a common alternative to using sedation in the NHS.

The model

The health outcome measure that NICE prefers for cost-effectiveness analysis is quality-adjusted life years (QALYs). It is not likely that the use of sedation techniques will lead to significant differences in QALYs as changes in health related quality of life will only occur over a short period of time. Sedation techniques may be associated with side effects but the GDG suggested that the events observed in the evidence review are not expected to lead to long-term effects that will result in significant QALY differences across different techniques. We therefore carried out a cost-minimisation analysis, that is, we assumed that the quality-adjusted life years would be the same for all treatment strategies.

The success rate of achieving a complete procedure with each technique was not assumed to be equivalent: in the event that a sedation technique fails it is assumed that the procedure would be rescheduled and conducted using general anaesthesia.

We have assessed costs from the perspective of the NHS and personal social services. In economic evaluation it is usual to put a lower weight on costs occurring in the future to reflect both the interest rate and people's time preference – a process known as discounting. However, in the case of this model, all of the included costs occur over a short time horizon and consequently there was no need to discount. The outcome of the analysis was the cost per patient for the whole pathway eventually leading to a successful completion of the procedure, so it includes the cost of the initial procedure plus the cost of any additional procedures required as a result of initial treatment failure.

The cost of sedation includes the time cost of personnel required for the induction and recovery from sedative drug or GA, as well as time cost of the personnel during the procedure. The cost of a strategy also includes the unit cost of drugs for sedation and GA, and the cost of consumables for administering them. We have not included the cost of equipment as it is assumed that these are already available at the point of service delivery and are used for other varied purposes. It would be difficult to estimate the fraction of the cost of equipment attributable to use of sedative drugs or GA.

Some strategies are associated with certain complications and the treatment of complications could result in additional costs.

In the model the expected cost of each strategy is conditional on the strategy's success rate and complication rate as well as the cost of the intervention itself. This can be represented by a decision tree; we present a separate decision tree for each population (see below).

The model was constructed using the best available evidence. Clinical and safety evidence was taken from a systematic review (see chapter 6 on clinical effectiveness and

safety review). When the evidence was weak or absent the GDG expert opinion was used to determine the input parameters of the model. The assumptions made in the model and the uncertainties in the input parameters are described explicitly. These were considered by the GDG when interpreting the model results. The impact of uncertainties in the model structure and input parameters were explored through deterministic sensitivity analyses. We did not do a probabilistic sensitivity analysis as the estimates for a number of key input parameters were ascertained by expert opinion. The limitations of the model are discussed.

Cost-effectiveness criteria

The technique with the lowest cost per patient is considered to be the optimal strategy from a cost-effectiveness perspective.

6.2 Dental procedures in children

6.2.1 Methods

Decision tree: The decision tree for the five strategies compared in this group is shown below (Figure 115). The use of any of the four sedative drugs (nitrous oxide plus oxygen, nitrous oxide plus sevoflurane, nitrous oxide plus iv midazolam, nitrous oxide plus sevoflurane plus iv midazolam) in a cohort of patients would lead to a successful completion of procedure in some patients. This is described as "success" on the decision tree. In other patients the drug would fail and the procedure would not be completed. In the event that the procedure was not completed, the patient would be given GA on a different occasion to enable the procedure to be completed. The sedative drugs are compared to GA. The GDG suggested that GA leads to completion of procedure in all the patients. Apart from N_2O plus iv midazolam, the GDG assumed that the sedative drugs are associated with vomiting in some patients. They GDG also assumed that the GA strategy is not associated with any complication. The basis for this assumption was that most side effects of GA in children are minor and that many safety measures are in place to minimise the risk of complications. The vomiting event at the branch of the tree for patients who failed to complete the procedure (failure), and who were eventually given GA, reflects the fact that the sedative drug leads to vomiting regardless of whether the procedure is completed (success) or not (failure).

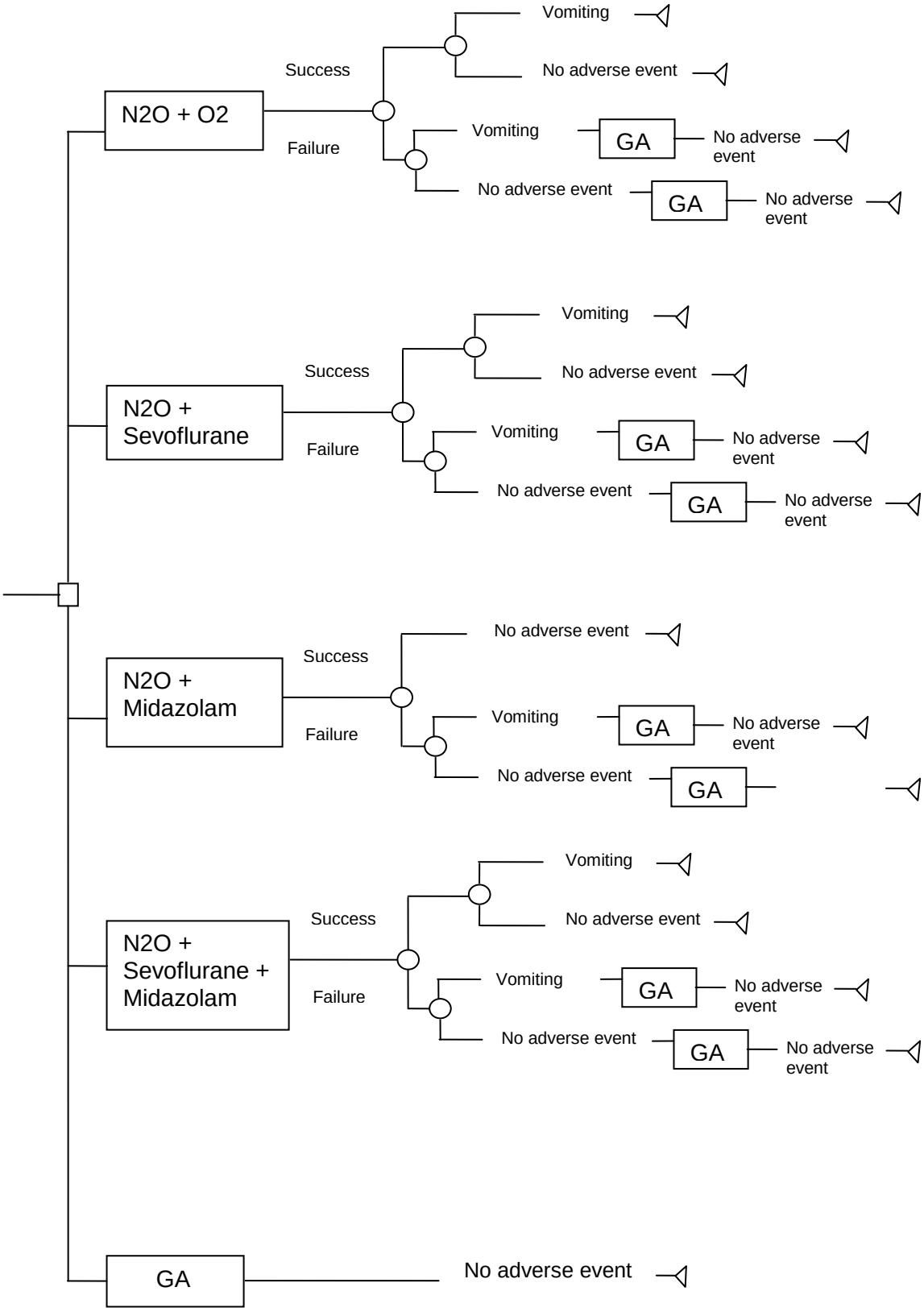

Figure 115. A decision tree of four sedative drugs compared to general anaesthesia in dental procedures in children

Table 1. Success rate of sedative drugs and general anaesthesia in dental procedures in children

Strategy	Success rate (%)	Source
N2O+O2	52.4	Lahoud & Averley 2002[23]
N2O+Sevoflurane	89.2	
N2O+Sevoflurane+iv midazolam	93.3	Averley 2004[3]
N2O+iv midazolam	79.7	
GA	100	GDG

Clinical data on success rate, complication rate and duration: The success rate of sedative drugs and GA are described in Table 1. There were two studies that assessed the use of sevoflurane and nitrous oxide in children[10,23].

The Lahoud study[23] assessed the efficacy of this drug combination in dental children and the De Sanctis Briggs study[10] assessed the safety in children undergoing MRI. The data on success rate was taken from the Lahoud study and the study has been described fully elsewhere (see chapter 6 the clinical effectiveness). It was an RCT of 411 anxious children undergoing dental procedures randomised to either 0.1 – 0.3% sevoflurane in 40% of N_2O or 40% of N_2O. The group that received sevoflurane plus nitrous oxide had significantly higher completion rate of 89% and this evidence was of moderate quality. There was only one study that assessed the efficacy of nitrous oxide plus sevoflurane plus intravenous midazolam in children[3]. The study has been described fully elsewhere (see chapter 6 on clinical effectiveness). It was an RCT of 697 anxious children undergoing dental procedures. Study participants were randomised to one of the three arms: 0.3% sevoflurane plus 40% nitrous oxide plus intravenous midazolam, or 40% nitrous oxide plus iv midazolam, or medical air plus intravenous midazolam. The sevoflurane plus nitrous oxide plus midazolam group had a significantly higher completion rate of 93.3% and this was used in the model. The combination strategy, nitrous oxide plus intravenous midazolam was also taken from the Averley study[3] and this combination was associated with a higher completion rate of 79.7% when compared to the medical air plus intravenous midazolam group. The evidence from the Averley study[3] was of moderate quality. There were a number of RCTs that assessed the efficacy of nitrous oxide and oxygen[13,34,41,46-50]. The Fauroux study[13] reported a completion rate but the evidence was low quality. The GDG felt that in clinical practice the patients receiving this sedative drug will have at least 50%. We used the success rate of 52.4% reported in the Lahoud study[23] for patients that received 40% nitrous oxide. The GDG also felt that the patients in the trials are not typical and the selection pattern may not be representative of clinical practice. If patients are assessed and selected for this strategy, success rate could be as high as 95%. We have therefore used 95% in sensitivity analysis. General anaesthesia was assumed to have a success rate of 100%.

The evidence from the systematic review on the timings for induction, procedure and recovery for the sedative drugs and GA was not complete, and when available, it was inconsistent with the GDG's clinical experience. They considered the timings reported in the review and suggested alternative plausible timings to be used in the model and this is shown in Table 2.

Table 2. Timings and vomiting rate for sedative drugs and GA in dental procedures in children

Strategy	Timing (minutes)			Vomiting rate (%)
	Induction	Procedure	Recovery	
N2O+O2	5	30	15	2
N2O+Sevoflurane	5	30	30	2
N2O+Sevoflurane+iv midazolam	15	30	45	2
N2O+iv midazolam	15	30	45	2
GA	10	30	30	

Vomiting rates were reported in the systematic review but these were also inconsistent and could not be used in a comparative way. We assumed a conservative a rate of 2% should be used for all the sedative drugs.

NHS staff required for application of strategy: The GDG suggested that the following NHS staff would be required during the induction, procedure and recovery phases of different strategies (Table 3. NHS staff required to apply sedative drugs and general anaesthesia in dental procedures in children*). We used £23 as the cost per hour for a nurse and anaesthetic assistant. This was based on the median full-time equivalent basic salary for "Agenda for Change Band 5 of the October-December 2007 NHS Staff Earnings" estimates for qualified nurses[40]. The rate for consultant dentist and anaesthetist was assumed to be equivalent to the average consultant (physician) earnings at the NHS and we used a rate of £122 per hour[40].

Table 3. NHS staff required to apply sedative drugs and general anaesthesia in dental procedures in children*

Strategy	Induction	Procedure	Recovery
N2O+O2	N + Den	N + Den	N
N2O+iv midazolam	N + Den	N + Den	N
N2O+Sevoflurane	N + Den	N + Den (x2)	N
N2O+Sevoflurane+iv midazolam	N + Den	N + Den (x2)	N
GA	ODA + A	N + Den + A + ODA	N

* N=Nurse, Den=Dentist, A=Anaesthetist, ODA=Anaesthetist Assistant, N2O=Nitrous oxide, GA=General Anaesthetic

Cost of drugs, consumables and complications: The unit cost of drugs is listed in table 4. We could not identify the cost of nitrous oxide and sevoflurane from the British National Formulary (BNF). The cost of nitrous oxide was estimated at £10 per patient by one of the GDG members using data from their primary care facility, and the additional cost of sevoflurane was £1 per patient. This was for gasses only and excludes the cost of the equipment to deliver the gasses, for scavenging or maintenance. The cost of intravenous midazolam was estimated at £0.87 assuming a maximum dose of 7.5mg (BNF: 5mg/mL, 2mL amp = 58p).

Table 4. Unit cost of drugs used in the model for dental procedures in children

Strategy	Route and Dose	Price	Source of price data
N2O+O2	Inhalation, 40% nitrous oxide and oxygen	£10.00	GDG
N2O+iv midazolam	Inhalation: 40% nitrous oxide Injection: Midazolam: max dose of 7.5mg	£10.87	GDG and BNF
N2O+Sevoflurane	Inhalation, 0.1 – 0.3% sevoflurane in 40% nitrous oxide	£11.00	GDG
N2O+Sevoflurane+iv midazolam	Inhalation: 0.3% sevoflurane in 40% nitrous oxide, Injection: Midazolam: max dose of 7.5mg	£11.87	GDG and BNF
GA	Propofol is used for induction. Induction dose: 2.5mg/kg, Maintenance dose: 0.1 – 0.3% sevoflurane in 40% nitrous oxide	£11.73	GDG and BNF

General anaesthesia was assumed to be induced with propofol and maintained with sevoflurane and nitrous oxide. Induction dose was 2.5mg per kilogram and a child of 25kg would require 62.5mg for induction. This would cost £0.73 (BNF prices: 1% injection (emulsion), 10mg/mL, net price 20-mL = £2.33). Maintenance would be 0.1 – 0.3% sevoflurane in 40% nitrous oxide and this would cost £11. The total cost of GA was therefore £11.73.

The GDG produced a list of consumables required for the administration of sedative drugs and GA. We have included the cost of these in the model. The list is shown below in Table 5 alongside their unit costs. The cost data were taken from the NHS purchase and supply chain catalogue[37]. Apart from the strategy, nitrous oxide plus oxygen, and nitrous oxide plus iv midazolam, all sedative drugs and GA would require all the consumables listed in the table. The GDG advised that the application of nitrous oxide plus oxygen and nitrous oxide plus iv midazolam would not require intravenous capnography and electrocardiographic electrodes but would require the other consumables in the table. We assumed that the treatment of vomiting would require 30 minutes of nurse's time.

Table 5. Type and unit cost of consumables included in the model for dental procedures in children

Consumables	Unit cost (£)
iv cannula	0.21
Capnography cannula	0.75
Oxygen mask	0.53
Pulse oximetry probe	7.29
Electrocardiographic electrodes	0.19
Laryngoscopes	4.02
Endotracheal tubes	1.65
Laryngeal masks	3.78
Guedel airways	0.23
Intubating bougie	7.40
Bag-valve mask	5.53

Sensitivity Analyses

We carried out a number of sensitivity analyses to test the robustness of model results to our model assumptions. We started by varying the success rates of the sedative drugs to determine the point at which the drug becomes cost saving compared to GA. The GDG felt that a success rate of 52.4% used in the base case for nitrous oxide would be low in patients who have been pre-selected to receive it and they advised that a rate of 95% be used in sensitivity analysis. The GDG advised that the induction time of 10 minutes used in the base case for GA should be increased to 15 minutes in a sensitivity analysis as induction time of this magnitude could be observed in some settings. In addition to its use as a sedative drug, nitrous oxide is used in combination with sevoflurane to maintain GA. In base case, we have used £10 as the cost per patient for using nitrous oxide. The GDG advised that this estimate could be an over-estimate in hospital care facility. It was therefore assumed that the cost of nitrous oxide per patient will be £5. In the other three sedation strategies, sedationist dentist would not be required for induction and during the procedure.

6.2.2 Results

The total cost per patient of each of the five strategies compared in the base case analysis for this population is given in

Table **6. Base case analysis: Cost per patient of different sedation strategies compared with general anaesthesia for dental procedures in children** below. N_2O + iv midazolam was the least expensive strategy at £213 per patient.

Drug costs and consumable costs varied little between strategies. Complication costs were negligible because the incidence was low for all strategies. The biggest component of cost was staff time (especially dentist and anaesthetist time). The cost of second line treatment also varied substantially between strategies, decreasing as the success rate increases.

N_2O+O_2 was more costly in the base case but this was because we had taken a very conservative approach to estimating efficacy (using the rate from a trial of very anxious children, 52%). If instead we assume a success rate of greater than 59% then it becomes cost saving in the model compared to GA – the GDG felt that a rate of 95% was more plausible. Another sedation strategy (Sevoflurane plus nitrous oxide plus iv midazolam) was more expensive than GA regardless of the success rate assumed. This was because it required a sedationist dentist in addition to the operating dentist.

Table 6. Base case analysis: Cost per patient of different sedation strategies compared with general anaesthesia for dental procedures in children

Strategy	Mean cost of 1st line						Mean cost of 2nd line	Total mean cost
	Drugs	Consum-ables	Anaes-thetist	Dentist	Nurse	Vomit-ing rate		
N20 + 02	£10	£31	£ -	£71	£19	£0.23	£107	£238
N20 + iv midazolam	£11	£31	£ -	£92	£35	£0.23	£45	£213
Sevoflurane + N20	£11	£32	£ -	£132	£25	£0.23	£24	£224
Sevoflurane + N20 + iv midazolam	£12	£32	£ -	£153	£35	£0.23	£15	£246
GA	£12	£32	£81	£61	£38			£224

The results of one-way sensitivity analyses are presented in Table 7 **Sensitivity analyses on the cost per patient of using different sedation strategies compared with general anaesthesia in dental procedures in children**† below. We started by varying the success rate of the sedative drug strategies to determine the point at which they become cost-saving compared to the GA strategy. For example, the strategy, nitrous oxide plus oxygen, was cost saving as long as the success rate of the sedative drug is equal to or greater than 59%. Sevoflurane plus nitrous oxide plus iv midazolam was not cost-saving even at a success rate of 100%.

When the success rate of all sedation techniques was increased to 95% for all strategies, N2O became the lowest cost strategy. Otherwise the results were robust to sensitivity analysis.

Table 7 Sensitivity analyses on the cost per patient of using different sedation strategies compared with general anaesthesia in dental procedures in children†

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate at which strategy becomes cost-saving compared to GA (%)	Mean cost when success rate of sedation = 95%	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡
N20 + 02	£238	52	59%	£142	£244	£233
N20 + iv midazolam	£213	80	75%	£179	£216	£208
Sevoflurane + N20	£224	90	90%	£211	£225	£225
Sevoflurane + N20 + iv midazolam	£246	93	*	£242	£247	£240
GA	£224	100	NA	**	£236	£219

NA=not applicable. *not cost-saving even at 100%, †pt=patient, ‡N2O is used in combination with sevoflurane to maintain general anaesthesia. ** Same as base case

6.3 Dental procedures in adolescents

6.3.1 Dental procedures in adolescents

Decision tree: The decision tree for the two strategies compared in this group is shown below (Figure 116. A decision tree of iv midazolam compared to general anaesthesia in dental procedures in adolescents). The application of intravenous midazolam in a cohort of patients would lead to successful completion of procedure in some patients. In other patients it would fail and the procedure would be completed using GA as a second line option. This strategy is compared with using GA as a first line option. General anaesthesia leads to completion of procedure in all the patients and is assumed not to be associated with any complications. Intravenous midazolam is associated with oxygen desaturation of less than 90%. The oxygen desaturation event at the branch of the tree for patients who failed to complete the procedure (failure), reflects the fact that intravenous midazolam leads to oxygen desaturation regardless of whether the procedure is completed or not.

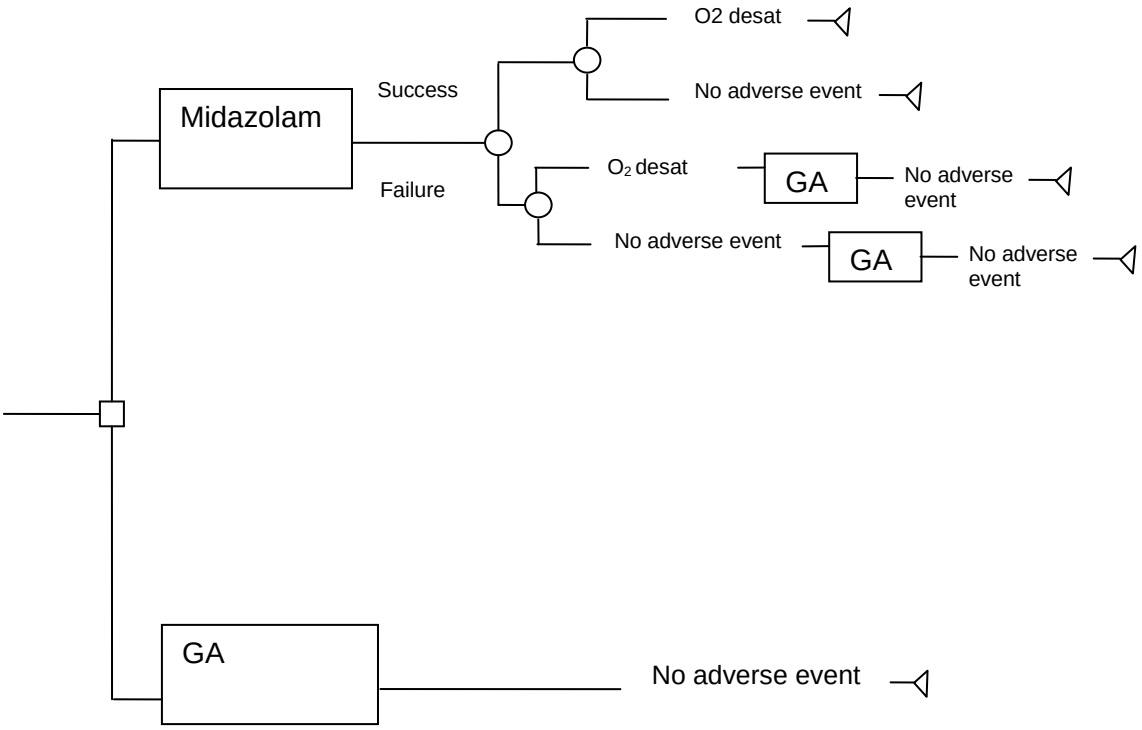

Figure 116. A decision tree of iv midazolam compared to general anaesthesia in dental procedures in adolescents

Clinical data on success rate, complication rate and duration: The success rate of intravenous midazolam and GA are given in Table 8. There was no directly applicable evidence from the review on the success rate for intravenous midazolam. Success rates of 95.2%, 78.9% and 100% were reported in three heterogeneous studies. The first figure was from a study of oral midazolam in children undergoing intravenous insertion[27]. The second estimate was from a study of intranasal midazolam in children undergoing venipuncture insertion[14]. The third estimate was from a study of oral and intranasal midazolam in children undergoing suture and laceration repair[8]. GDG consensus was that a success rate of 95% be used in the model for this group.

Table 8. Success rate of sedative drugs and general anaesthesia in dental procedures in adolescents

Strategy	Success rate (%)	Source
iv midazolam	95	GDG
GA	100	GDG

There was no applicable evidence on the duration of the strategies. The GDG considered the existing evidence from the clinical effectiveness review and made timing estimates that reflect their clinical experience. They suggested that the following estimates should be used in the model (Table 9).

Table 9 Timing for sedative drugs and GA in dental procedures in adolescents

Strategy	Timing (minutes)		
	Induction	Procedure	Recovery
iv midazolam	15	60	45
GA	10	60	30

NHS staff required for application of strategy: The GDG suggested that the following NHS staff would be required during the induction, procedure and recovery phases of the two strategies (Table 10). The unit cost of time spent by the nurse, dentist, anaesthetist and anaesthetist assistant has been described above in the section on "NHS staff required for application of strategy" under "Dental procedure in children".

Table 10 NHS staff required to apply sedative drug and general anaesthesia in dental procedures in adolescents*

Strategy	Induction	Procedure	Recovery
iv midazolam	N + Den	N + Den	N
GA	ODA + A	N + Den + A + ODA	N

* N=Nurse, Den=Dentist, A=Anaesthetist, ODA=Anaesthetist Assistant, N2O=Nitrous oxide, GA=General Anaesthetic

Cost of drugs, consumables and complications: The cost of intravenous midazolam and GA used in the model was £0.87 and £11.73 respectively. We have described how these were arrived at in the section on 'Cost of drugs, consumables and complications' under 'Dental procedures in children'. The GDG advised that the application of intravenous midazolam would not require iv capnography and electrocardiographic electrodes but would require the other consumables in Table 5 above. The cost of consumables for intravenous midazolam was estimated at £31, and for GA, £32. The cost of GA includes the cost of all consumables listed above in Table 5. Oxygen desaturation that is less that 90% is a complication associated with midazolam. Some other interventions considered in this economic analysis are also associated with this complication. The GDG decided that this was unlikely to be associated with a treatment cost.

6.3.2 Results

We have compared two strategies in this group and the total cost per patient in the base case analysis for each of them is shown in Table 11 below. Midazolam was less expensive at £248.

The cost of consumables was similar for both strategies but the cost of drugs was more for the GA strategy. The biggest component of cost was staff time (especially dentist and anaesthetist time).

Table 11. Base case analysis: Cost per patient of using iv midazolam compared with general anaesthetia in dental procedures in adolescent

Strategy	Mean cost of 1st line					Mean cost of 2nd line
	Drugs	Consum-ables	Anaes-thetist	Dentist	Nurse	
iv midazolam	£1	£31	£ -	£153	£46	£18
GA	£12	£32	£142	£122	£61	

We have described the results of one-way sensitivity analyses in Table 12 below. The cost per patient of the midazolam remained lower than the cost of the GA as long as the success rate of midazolam is not below 63%. Midazolam remained associated with lower costs for all the sensitivity analyses conducted.

Table 12 Sensitivity analyses on the cost per patient of using iv midazolam compared with general anaesthesia in dental procedures in adolescents †

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate at which strategy becomes cost-saving compared to GA (%)	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡	Mean cost with nurse-led sedation
iv midazolam	£248	95	63	£249	£248	£218
GA	£369	100	Not applicable	£381	£364	Same as basecase

†pt=patient, ‡ N2O is used in combination with sevoflurane to maintain general anaesthesia

6.4 Sensitivity Analyses

The robustness of the results to our model assumptions was tested using sensitivity analyses. We varied the success rate of intravenous midazolam to determine the point at which the drug becomes more cost saving compared to GA. We also increased the induction time of GA to 15 minutes from 10 minutes as the GDG suggested that an induction time of this magnitude could be observed in some settings. Nitrous oxide is used in combination with sevoflurane to maintain GA. The GDG suggested that the cost of nitrous oxide used in the base case analysis could be an over-estimate in a hospital care facility and in a sensitivity analysis, we assumed that the cost of nitrous oxide per patient would be £5. Short painful procedures

6.4.1 Methods

Decision tree: The decision tree for the three strategies compared in this group is shown below (Figure 117). The application of intravenous ketamine or intravenous fentanyl plus propofol in a cohort of patients would lead to successful completion of procedure in some patients. In others the drug would fail and the procedure would be completed using GA as a second line option. These strategies are compared to using GA as a first line option. General anaesthesia leads to completion of procedure in all the patients and is assumed not to be associated with complications. Intravenous ketamine is associated with vomiting, and both of the sedative drug strategies compared in this group are associated with hypotension and respiratory complications as well as with oxygen desaturation less than 90%.

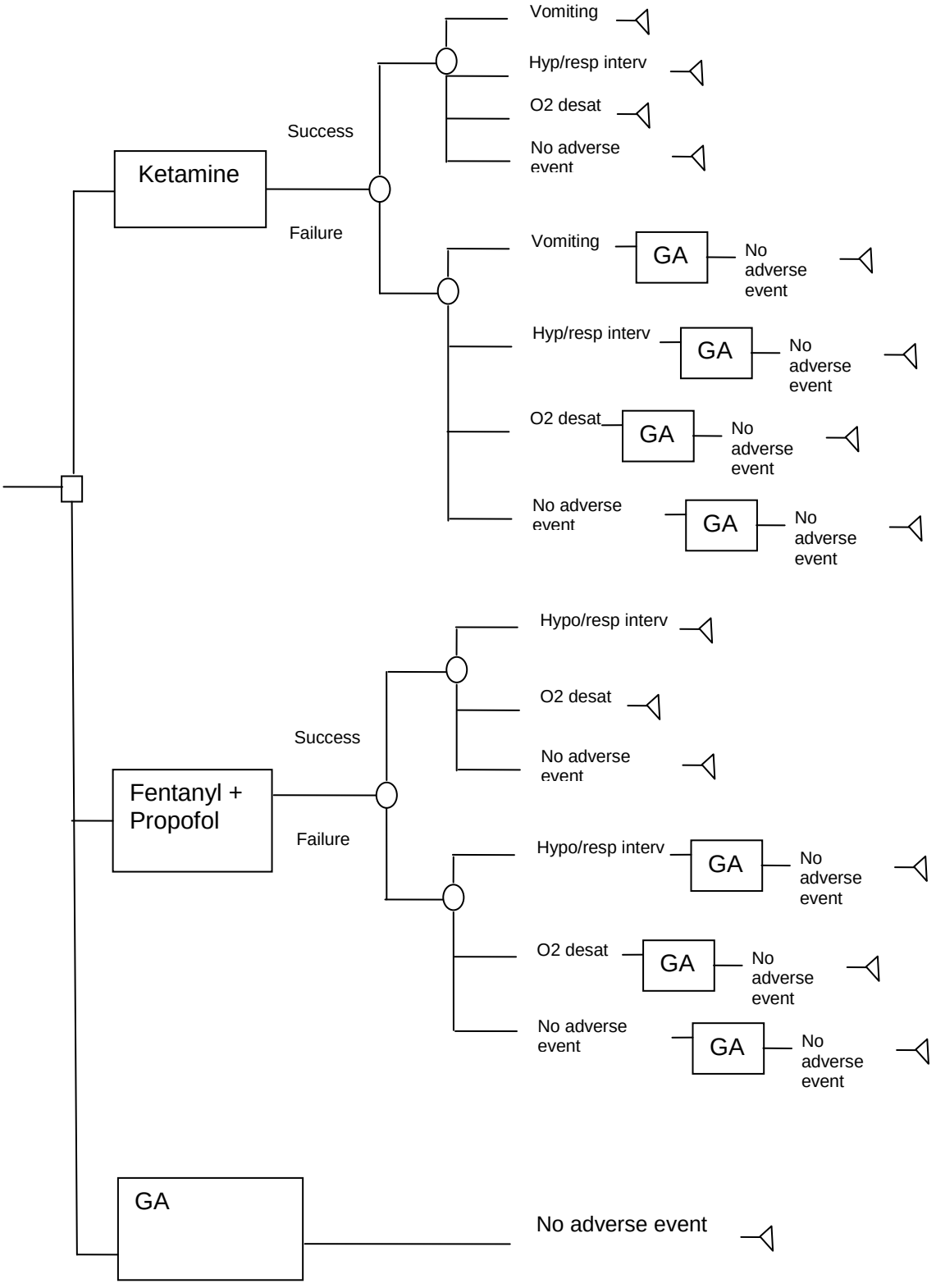

Figure 117. A decision tree of two sedative drugs compared to general anaesthesia in short painful procedures

Clinical data on success rate, complication rate and duration: The success rates of the sedative drugs and GA are described in Table 13. There was no evidence on the appropriate success rate to apply in the model for intravenous ketamine. The GDG was of the view that up to 1% of procedures are not successfully completed under ketamine sedation. They advised that a success rate of 99% should be used in the model. They suggested that the 100% reported in Cechvala 2008[7] for intravenous fentanyl plus propofol was clinically credible, and this rate was used in the model.

Table 13 Success rate of sedative drugs and general anaesthesia in short painful procedures

Strategy	Success rate (%)	Source
Ketamine	99	GDG
Fentanyl+propofol	100	Cechvala 2008[7]
GA	100	GDG

The Cechvala study[7] was an RCT carried out in 22 children undergoing lumbar puncture for diagnosis of acute leukaemia or lymphoma. It compared intravenous fentanyl (1mcg/kg) plus intravenous propofol (1-2mg/kg/min) plus oxygen supplementation plus topical anaesthesia with placebo (normal saline) plus intravenous propofol (1-2mg/kg/min) plus oxygen supplementation plus topical anaesthesia. All study patients completed the procedure and this evidence was judged as moderate quality. General anaesthesia was assumed to have a success rate of 100%. Vomiting and oxygen desaturation rate less than 90% were reported for ketamine in several heterogenous studies included in the systematic review of efficacy and the GDG advised that a rate of 6.65% for vomiting and 0.9% for oxygen desaturation rate less than 90% should be taken from the study with the largest sample size[16]. They also suggested from their clinical experience that ketamine would be associated with up to one percent rate of hypotension and respiratory intervention. Hypotension and respiratory intervention rate of 18% was reported in only the Cechvala study[7] for intravenous fentanyl plus propofol, and this rate was used in the model. The rate of oxygen desaturation less than 90% was reported as 5% in one study[4]. These studies have been described in the sections on the efficacy and safety of sedation techniques.

After considering the limited evidence from the review the GDG provided the following estimates as the timings for the three strategies (Table 14).

Table 14 Timings and vomiting rate for sedative drugs and GA in short painful procedures

Strategy	Timing (minutes)		
	Induction	Procedure	Recovery
Ketamine	10	30	30
Fentanl+propofol	10	30	30
GA	10	30	30

NHS staff required for application of strategy: The GDG suggested that the following NHS staff would be required during the application of the three strategies compared here (Table 15). The unit cost of the time spent by the personnel has been described above (dental procedure in children).

Table 15 NHS staff required to apply sedative drug and general anaesthesia in short painful procedures

Strategy	Induction	Procedure	Recovery
Ketamine	N + D	N (x2) + D	N
Fentanyl+propofol	N + D	N (x2) + D (x2)	N
GA	ODA + A	N + D + A + ODA	N

* N=Nurse, D=Physician, A=Anaesthetist, ODA=Anaesthetist Assistant, GA=General Anaesthetic

Cost of drugs, consumables and complications: We assumed a median dose of 30mg for ketamine[42]. This would cost £0.76 (BNF: 10mg/mL, 20-mL vial = £5.06). The dosage in Cechvala 2008[7] for intravenous fentanyl was 1mcg/kg. For a 25 kg child requiring 25mcg, it would cost £0.14 (BNF: 50mcg/mL, net price 2-mL amp = 54p). The dosage for propofol in Cechvala 2008[7] was 1-2mg/kg/min infusion. We assumed that 25kg child would require 38mg for one minute. The child would require about 4mL which would cost £0.46. (BNF: 1% injection (emulsion), 10mg/mL. net price 20-mL amp = £2.33). The total cost of administering this combination therapy would therefore be £0.60. The cost of GA used in the model was £11.73, and the cost of consumables for all strategies was £32. A description of how these were arrived at has been given above (dental procedure in children). The cost of consumables includes the cost of all consumables listed above in Table 5.

Oxygen desaturation that is less than 90% is a complication associated with the sedative drugs compared in this group but there would be no additional treatment cost for this. We assumed that 30 minutes of nurse's time would be required both for the treatment of vomiting and for hypotension and respiratory interventions.

Sensitivity Analyses

A number of sensitivity analyses were done to test the robustness of the model results. We varied the success rates of the two sedative drug strategies to determine the point at which any of the strategies becomes more cost saving compared to GA. We did the same sensitivity analyses described in the section for dental procedures in adolescents regarding GA induction time, cost of nitrous oxide and the nurse as the only personnel required for the application of sedative drugs. In the case of ketamine and fentanyl plus propofol, sedationist physician would not be required for induction. In the case of fentanyl plus propofol, only one physician would be required during the procedure.

6.4.2 Results

The average cost of the strategies compared in this model population in the base case analysis is given below in Table 16. Ketamine was the least expensive strategy at £155, and GA was the most expensive strategy at £224.

The cost of consumables for the three strategies was the same but the cost of the GA drugs was higher than the cost of the sedative drugs. The highest cost component was the cost of staff time, particularly the cost of physician and anaesthetist time. Fentanyl plus iv midazolam was actually more expensive than ketamine because it required a sedationist dentist in addition to an operating dentist for its administration.

The complication costs associated with ketamine were low because of low incidence while the cost of complications associated with fentanyl plus propofol was slightly higher because of higher incidence.

Table 16 Base case analysis: Cost per patient of using sedation strategies compared with general anaesthesia in short painful procedures

Strategy	Mean cost of 1st line							Mean cost of 2nd line	Mean cost
	Drugs	Consu-mables	Anaes-thetist	Physi-cian	Nurse	Vomi-ting rate	Hypo / Resp interv-ention		
Ketamine	£1	£32	£ -	£81	£38	£0.77	£0.13	£2	£155
Fentanyl + Propofol	£1	£32	£ -	£142	£38	£ -	£2.09	£ -	£215
GA	£12	£32	£81	£61	£38				£224

The results of one-way sensitivity analyses are presented in Table 17 below. We varied the success rate of the sedative drug strategies to determine the point at which they become cost-saving compared to GA strategy. Ketamine remained cost saving as long as the success rate of using it is not below 69%. The combination drug, fentanyl plus propofol remained cost-saving as long as the success rate of the drug combination is not below 95%.

Ketamine remained the cost-saving compared with the other strategies when the GA induction time is 15 minutes or the cost of nitrous oxide is £5. Unlike ketamine, the other two strategies require physician sedationist in addition to operating physician and this makes it less expensive. When we assumed that sedation was administered by a nurse, fentanyl plus propofol became cost-saving when compared with ketamine and GA.

Table 17 Sensitivity analyses on the cost per patient of using different sedation strategies compared with general anaesthesia in short painful procedures †

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate at which it becomes cost-saving compared to GA (%)	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡	Mean cost with nurse-led sedation
Ketamine	£155	99	69	£155	£155	£135
Fentanyl + Propofol	£215	100	95	Same as basecase	Same as basecase	£134
GA	£224	100	Not applicable	£236	£219	Same as basecase

†pt=patient, ‡ N2O is used in combination with sevoflurane to maintain general anaesthesia

6.5 Painless imaging procedures

6.5.1 Methods

Decision tree: The decision tree for the two strategies compared in this group is shown below (Figure 118). The use of high dose chloral hydrate as a sedative drug in a cohort of patients would lead to successful completion of procedure in some patients, and in others it would fail. In the event of failure, the procedure would be completed using GA as a second line treatment option. This strategy is compared to using GA as a first line option to enable completion of procedure. General anaesthesia is assumed to lead to completion of procedure in all the patients and would not to be associated with any complication. High dose chloral hydrate is associated with vomiting.

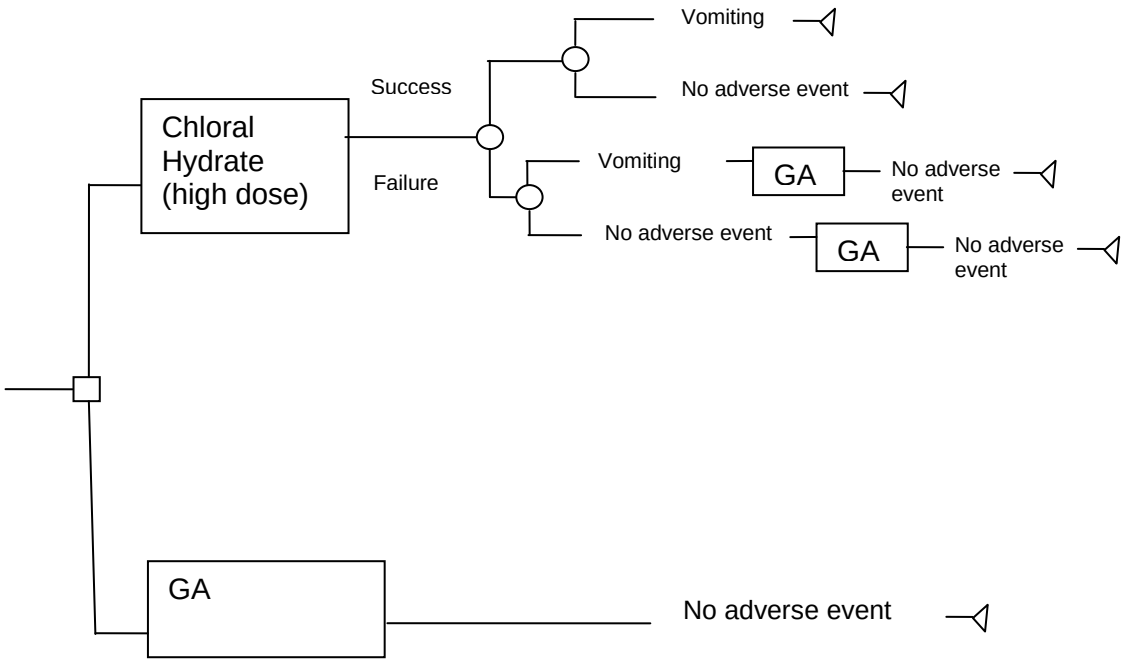

Figure 118. A decision tree of chloral hydrate compared to general anaesthesia in painless imaging procedures

Clinical data on success rate, complication rate and duration: The success rate of oral chloral hydrate was reported in two studies[18,32]. The Marti-Bonmati study[32] was carried out in children undergoing MRI and the Houpt study[18] was in children undergoing dental procedure. The GDG felt that the success rate reported in the former study should be used as it is a more applicable study for this model group. The Marti-Bonmati study[32] has been described before in the section on clinical effectiveness and safety. In the study, high dose chloral hydrate (96mg/kg) was compared to intermediate dose (70mg/kg). It was reported that high dose chloral hydrate had a completion rate of 100% and we have used this rate in the model. The study was judged to be of moderate quality. We have assumed the success rate of GA to be 100%.

Table 18 Success rate of sedative drugs and general anaesthesia in painless imaging procedures

Strategy	Success rate (%)	Source
Chloral hydrate (high dose)	95	Marti-Bonmati 1995[32]
GA	100	GDG

After considering the evidence on the timings reported in the review the GDG suggested that it would be more clinically realistic to use the following timings in the model.

Table 19 Timing for sedative drugs and GA in painless imaging procedures

Strategy	Timing (minutes)		
	Induction	Procedure	Recovery
Chloral hydrate (high dose)	20	50	40
GA	10	50	30

NHS staff required for application of strategy: The GDG also suggested that the following NHS staff would be required during the different phases of applying the two strategies (Table 20). The unit cost of time spent by the personnel has been described above (dental procedure in children). We used £29 as the cost per hour for a radiographer. This was based on the median full-time equivalent basic salary for "Agenda for Change Band 5 of the October-December 2007 NHS Staff Earnings" estimates[40].

Table 20 NHS staff required to apply sedative drug and general anaesthesia in painless imaging procedures*

Strategy	Induction	Procedure	Recovery
Chloral hydrate (high dose)	N + D	N + D + R	N
GA	ODA + A	N + A + ODA	N

N=Nurse, D=Physician, A=Anaesthetist, ODA=Anaesthetist Assistant, R=Radiographer, GA=General Anaesthetic

Cost of drugs, consumables and complications: The maximum dose of chloral hydrate in the BNF is 2g (BNF, cloral betaine 707mg (=chloral hydrate 414mg): net price 30-tab pack =£7.90). A maximum of five tablets would cost £1.32. The cost of GA used in the model was £11.73 and we have described elsewhere how we arrived at this figure (dental procedure in children). The cost of consumables for each of the two strategies compared here was £32. This included the cost of all consumables listed above in Table 5. The treatment cost of vomiting was assumed to be equivalent of 30 minutes of nurse's time.

Sensitivity Analyses

In order to test the robustness of the model for chloral hydrate and GA, we carried out the same set of sensitivity analyses described above in the section on short painful procedures. We conducted a sensitivity analysis to explore the impact on the result of assuming a success rate of 95% for high dose chloral hydrate. We assumed that a sedationist physician would not be required for induction of high dose chloral hydrate.

6.5.2 Results

We compared two strategies in this population and the result of the base case analysis showed that GA was less expensive at £224 than high dose chloral hydrate (Table 21). This was not surprising as the administration of the sedative drug requires a physician unlike the administration of GA.

The highest cost component of these strategies remained the cost of staff time especially physician and anaesthetist time. The cost of complication was low because of low incidence. The cost of consumables for the two strategies was the same but the cost of GA drugs was higher.

Table 21 Base case analysis: Cost per patient of high dose chloral hydrate compared with general anaesthesia in painless imaging

Strategy	Mean cost of 1st line							Mean cost
	Drugs	Consu-mables	Anaes-thetist	Physi-cian	Nurse	Radio-grapher	Vomit-ing rate	
Chloral hydrate (high dose)	£1	£32	£ -	£142	£42	£24	£0.03	£242
GA	£12	£32	£122	£ -	£35	£24		£224

The results of one-way sensitivity analyses are presented in Table 22 below. We changed the success rate of high dose chloral hydrate and, at 95% this strategy was even more expensive. Other results of the sensitivity analysis suggest that the GA strategy would be associated with less cost. The sedative drug strategy became less expensive only when the nurse was the only personnel that will apply the sedative drug.

Table 22 Sensitivity analyses on the cost per patient of using high dose chloral hydrate compared with general anaesthesia in short painless imaging †

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate of chloral hydrate = 95%	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡	Mean cost with nurse-led sedation
Chloral hydrate (high dose)	£242	100	£252	Same as basecase	Same as basecase	£201
GA	£224	100	Same as basecase	£236	£219	Same as basecase

†pt=patient, ‡ N2O is used in combination with sevoflurane to maintain general anaesthesia

6.6 Oesophago-gastroscopy

6.6.1 Methods

Decision tree: We compared intravenous midazolam and GA and the decision tree is the same as the one used to compare intravenous midazolam and GA in dental procedures in adolescents (Figure 116. A decision tree of iv midazolam compared to general anaesthesia in dental procedures in adolescents). The use of intravenous midazolam in a cohort of patients would lead to a successful completion of the procedure in some patients but would fail in others. In the patients where it failed, GA would be used to complete the procedure. The use of GA as a first line option would lead to completion of procedure in all patients. Intravenous midazolam is associated with oxygen desaturation level less than 90% and GA is assumed not to be associated with complications.

Clinical data on success rate, complication rate and duration: There was no directly applicable evidence from the review on the success rate for intravenous midazolam in patients undergoing oesophago-gastroscopy. Indirect evidence from three heterogeneous studies was considered by the GDG[8,14,27]. The first study was on oral midazolam in children undergoing intravenous insertion, and reported a success rate of 95.2%. The second was on intranasal midazolam in children undergoing venipuncture insertion, and reported a rate of 78.9%. The last study was on oral and intranasal midazolam in children undergoing suture and laceration repair, and reported a rate of 100%. The GDG agreed that a rate of 95% be used in the model. A success rate of 100% was used for GA. There was also no directly applicable evidence on the duration of the strategies for this group. The GDG considered other estimates reported in the review and made timing estimates that reflect their clinical experience. They suggested the estimate in the table below should be used (Table 23).

Table 23 Timings for sedative drugs and GA in oesophago-gastroscopy

Strategy	Timing (minutes)		
	Induction	Procedure	Recovery
iv midazolam	10	15	45
GA	10	15	30

NHS staff required for application of strategy: The GDG suggested that the following NHS staff would be required during the application of the strategies (Table 24). The unit cost of the time spent by the staff is described above (dental procedure in children).

Table 24 NHS staff required to apply sedative drug and general anaesthesia in oesophago-gastroscopy *

Strategy	**Induction**	**Procedure**	**Recovery**
Ketamine	N + D	N (x2) + D	N
GA	ODA + A	N + D + A + ODA	N

* N=Nurse, D=Physician, A=Anaesthetist, ODA=Anaesthetist Assistant, GA=General Anaesthetic

Cost of drugs, consumables and complications: The cost of intravenous midazolam and GA used are £0.87 and £11.73 respectively and a description of how we arrived at these estimates is given above (dental procedure in children). The cost of consumables for the two respective strategies is £31 and £32. The GDG advised that the application of intravenous midazolam would not require intravenous capnography and electrocardiographic electrodes but would require the other consumables in Table 5 above. The cost of consumables for GA includes the cost of all consumables listed above in Table 5. Oxygen desaturation less than 90% would not be associated with additional treatment cost.

Sensitivity Analyses

In order to test the robustness of the model, we carried out the same set of sensitivity analyses described above in the section on dental procedure in adolescents. We assumed that a sedationist physician would not be required for the induction of iv midazolam.

6.6.2 Results

There were two strategies compared in this population and the total cost per patient in the base case analysis is given in Table 25 below. Midazolam was less expensive at £122.

The cost of consumables was similar but drug cost was higher for GA. The highest cost component was cost of staff time particularly physician and anaesthetist time.

Table 25 Base case analysis: Cost per patient of using iv midazolam compared with general anaesthesia in oesophago-gastroscopy

Strategy	Mean cost of 1st line					Mean cost of 2nd line	Mean cost
	Drugs	Consum-ables	Anaes-thetist	Physi-cian	Nurse		
iv midazolam	£1	£31	£ -	£51	£33	£8	£122
GA	£12	£32	£51	£31	£27		£151

The results of one-way sensitivity analyses are described in Table 26 below. The cost per patient of the iv midazolam strategy remained lower than the cost of the GA strategy as long as the success rate of midazolam strategy is not below 75%. The midazolam strategy remained associated with lower costs for all the sensitivity analyses conducted.

Table 26 Sensitivity analyses on the cost per patient of using iv midazolam compared with general anaesthesia in oesophago-gastroscopy †

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate at which it becomes cost-saving compared to GA (%)	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡	Mean cost with nurse-led sedation
iv midazolam	£122	95	75	£123	Same as basecase	£102
GA	£151	100	Not applicable	£164	£146	Same as basecase

†pt=patient, ‡ N2O is used in combination with sevoflurane to maintain general anaesthesia

6.7 Colonoscopy

6.7.1 Methods

Decision tree: The decision tree that was used for the model for this group is shown below (Figure 119). The use of the combination technique, intravenous midazolam plus intravenous fentanyl in a cohort of patients would lead to a successful completion of the procedure in some patients but would fail in others. In the patients where it fails, GA would be used to complete the procedure. The use of GA as a first line option would lead to completion of procedure in all patients. The combination technique is associated with vomiting and oxygen desaturation less than 90%.

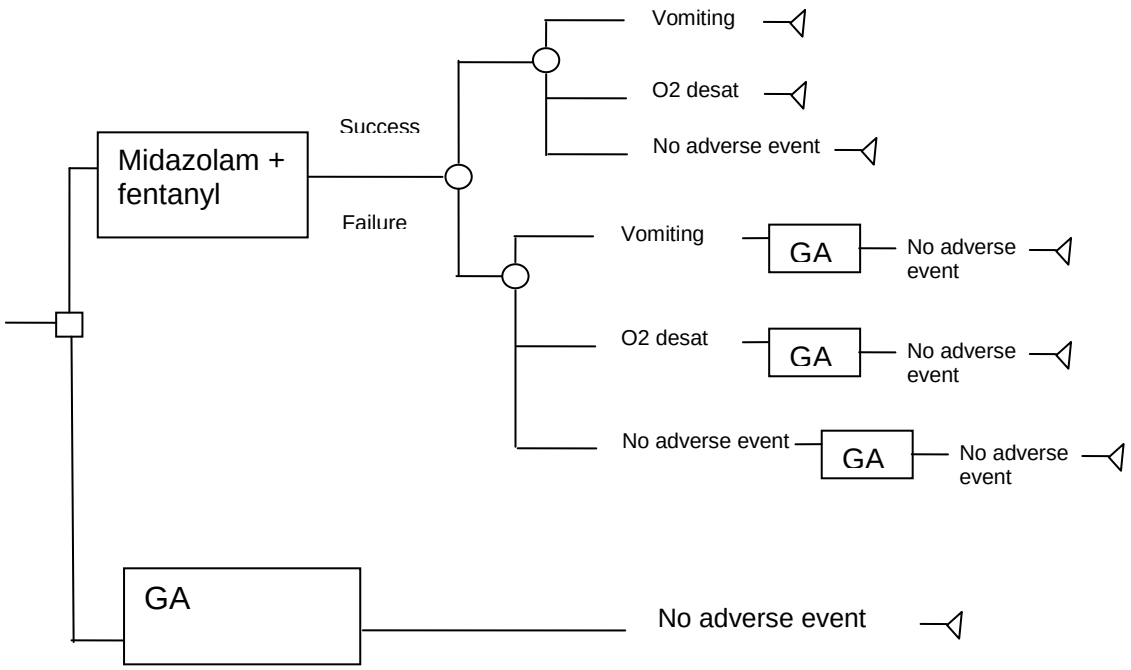

Figure 119 A decision tree of a combination sedation technique compared to general anaesthesia in colonoscopy

Clinical data on success rate, complication rate and duration: There was no directly applicable study in the systematic review that reported the success rate for this drug combination. Indirect evidence from one study was considered[29]. The study compared intravenous fentanyl plus midazolam with intravenous midazolam plus ketamine in 57 children undergoing placement of intravenous line. All patients were reported to have completed the procedure. The consensus was that a rate of 95% is a clinically realistic rate and should be used in the model. A success rate of 100% for GA was assumed. There were a number of heterogeneous studies on the safety of the combination sedation option and the GDG advised that we use rates from the study with largest sample size. A rate of 5.22% was reported for vomiting[38], and 2.56% for oxygen desaturation less than 90%[31].

There were no directly applicable timing estimates for the strategies and the following estimates were made based on the clinical experience of the GDG (Table 27).

Table 27 Timings for sedative drug and GA in colonoscopy

Strategy	Timing (minutes)		
	Induction	Procedure	Recovery
iv midazolam+fentanyl	10	45	45
GA	10	45	30

NHS staff required for application of strategy: The following NHS staff in Table 28 below was suggested by the GDG to be required for the application of the strategies. The unit cost of time spent by the personnel has been described above (dental procedure in children).

Table 28 NHS staff required to apply sedative drug and general anaesthesia in colonoscopy*

Strategy	Induction	Procedure	Recovery
iv midazolam+fentanyl	N + D	N (x2) + D	N
GA	ODA + A	N + D + A + ODA	N

* N=Nurse, D=Physician, A=Anaesthetist, ODA=Anaesthetist Assistant, GA=General Anaesthetic

Cost of drugs, consumables and complications: The cost of midazolam plus fentanyl was estimated based on the dosage reported in Lucas da Silva 2007[29] (midazolam, 0.15mg per kg; fentanyl, 1µg per kg). We assumed a maximum dose of 7.5mg reported in the BNF for midazolam which would cost £0.87. For a child 25kg, 25µg fentanyl would cost £0.14 (BNF for fentanyl: 50mcg/mL, net price 2-mL amp = 54p; BNF for midazolam: 5mg/mL, 2mL amp = 58p, 7.5mg would cost 87p). The total cost of this drug combination used in the model was therefore £1.01. The cost of GA was £11.73 and we have described how we arrived at this (dental procedure in children). The cost of consumables for each of the respective strategies was £32. This includes the cost of all consumables listed above in Table 5. The treatment cost of vomiting was assumed to be equivalent of 30 minutes of nurse's time.

Sensitivity Analyses

The robustness of the model results to our assumptions was tested using the same set of sensitivity analyses described above for gastroscopy. We assumed that a sedationist physician would not be required for the induction of iv midazolam plus fentanyl.

6.7.2 Results

The total cost per patient for each of the two strategies compared in this population in the base case analysis is given in Table 29 below. The combination strategy, iv midazolam plus fentanyl, was less expensive at £215.

The cost of GA drug was higher but the cost of consumables for both strategies was the same. The greatest cost component was the cost of staff time especially anaesthetist and physician time. The cost of complication was low because of low incidence.

Table 29 Base case analysis: Cost per patient of using iv midazolam plus fentanyl compared with general anaesthesia in colonoscopy

Strategy	Mean cost of 1st line						Mean cost of 2nd line	Mean cost
	Drugs	Consum-ables	Anaes-thetist	Physi-cian	Nurse	Vomit-ing rate		
iv midazolam + Fentanyl	£1	£32	£ -	£112	£56	£0.60	£15	£215
GA	£12	£32	£112	£92	£50			£296

We have described the results of one-way sensitivity analyses in Table 30 below. We varied the success rate of the combination strategy to determine the point at which it becomes cost-saving compared to GA strategy. The combination strategy is cost saving as long as the success rate of using it is equal to or greater than 68%. The combination strategy remained cost saving compared to the GA strategy for all the sensitivity analyses conducted here.

Table 30 Sensitivity analyses on the cost per patient of using iv midazolam plus fentanyl compared with general anaesthesia in colonoscopy †

Strategy	Mean cost (base case)	Success rate in base case (%)	Success rate at which it becomes cost-saving compared to GA (%)	Mean cost when induction time of GA = 15mins	Mean cost when cost of N2O = £5 ‡	Mean cost with nurse-led sedation
iv midazolam + fentanyl	£215	95	68	£216	Same as basecase	£195
GA	£296	100	Not applicable	£309	£291	Same as basecase

†pt=patient, ‡ N2O is used in combination with sevoflurane to maintain general anaesthesia

6.8 Discussion

We have attempted to evaluate the economic impact of using different sedation strategies, and we have compared the use of these strategies to the use of general anaesthesia (GA). We included staff costs, costs of drugs and consumables, complication costs and cost of sedation failure. We found that sedation is clearly cost-saving compared to GA in cases where the operating physician or dentist is able to administer sedation without the addition of a sedationist physician or dentist (typically for minimal and moderate sedation). In this case, quite a low success rate is required for sedation to be cost-saving.

In cases where the addition of a sedationist physician or dentist is required (typically for deep sedation), sedation could still be cost saving but this will depend primarily on

- The facility and equipment costs: We have not captured this in our analysis. It is particularly important when evaluating sedation techniques being carried out in primary care (for example dental procedures). However, facility costs may also be cheaper in A&E, for example, compared to a surgical theatre.

- The success rate: As the success rate gets lower, the cost of a sedation strategy increases.

- The speed at which the operation can be conducted under each technique: It seems unclear whether procedures can be delivered more or less quickly with sedation techniques.

Data in these areas seems to be lacking. The economic analysis we have carried out has a number of limitations and these were considered by the GDG when interpreting the results of the analysis. If facility costs do not vary between settings, then by omitting them we have biased our findings in favour of sedation because we have omitted them from the second line treatment. Second line treatment would require additional facility cost as this would happen on a different occasion. However, in evaluating sedation in primary dental care, the facility costs are likely to be far less and in this case, it is likely that the model biases in favour of GA.

Careful patient selection for sedation is important as this will optimise success rates and consequently both improve patient outcomes and minimise costs. The success rates we used in some of our analyses were not based on direct randomised controlled trial results. This was either where there was no trial data or where the available data was judged by the GDG as inapplicable. At these instances the GDG considered the available evidence and used expert opinion to inform the most appropriate rate that was used in the model. The GDG reported that very high rates of success (above 95%) are achievable with all techniques if patients are selected carefully. We used deterministic sensitivity analyses to explore the impact of alternative success rate on the model results.

The timing used in the model was based on the GDG's expert opinion. The GDG considered any existing timing data reported in the clinical review. There were discussions regarding claims that procedures can be conducted quicker under GA than using sedation but the evidence is unclear. The timing of sedation and GA strategies is an area that might benefit from further research.

There may be rare but serious complications arising from anaesthesia or sedation but these were not found in the evidence from the safety review (see chapter 6 on clinical effectiveness and safety review). The GDG felt that we need not include the impact of GA complications as most side effects are minor, especially in children, and that many safety measures are in place to minimise the risk of complications. Given the rarity of serious complications, we think it reasonable to omit the cost and health loss associated with these events.

We have not estimated quality-adjusted life years but we think this unlikely to affect our conclusions. There will be some disutility (reduced health related quality of life) associated with sedation failure. However, these changes will occur over a short period of time and therefore differences in mean quality-adjusted life years between strategies are likely to be negligible.

The impact of uncertainty in model input parameters on model results can be explored using probabilistic sensitivity analysis. We have not conducted this analysis on this occasion. However, we do not feel that this is a serious omission given that the model has been built mainly on expert opinion and therefore it is difficult to accurately ascertain the distribution and variances for a number of model parameters. Furthermore, we have done a number of deterministic sensitivity analyses in areas where we felt that alternative model assumptions could impact on results.

In one of the studies included in the economic review[43], it was suggested that sedation would cost less than GA. Nitrous oxide in oxygen was suggested to be less expensive than GA for dental procedure in children[5]. In another study[39], for children requiring manipulation of a forearm fracture in the emergency department, propofol plus fentanyl was compared with ketamine plus iv midazolam, fentanyl plus iv midazolam, and axillary approach to brachial plexus regional block with midazolam premedication. Propofol plus fentanyl was found to be the dominant strategy because it had the lowest cost and the shortest emergency department duration. However, these three studies were considered as having potentially serious limitations. Another study[20] also suggested that sedation is cheaper than GA in children undergoing dental procedure. This study was judged as having minor limitations and could be considered to be directly applicable to the UK NHS dental services.

In summary, the economic model has allowed a comparison of relevant interventions in different populations groups and has produced results that are directly applicable. Sedation strategies are likely to be cost-saving compared with general anaesthesia. The cost of drugs is less important than the cost of the staff involved. The most cost-effective sedation technique is likely to be those that don't require the addition of a sedationist physician or dentist, essentially those with a wider margin of safety. It will also depend on appropriate patient selection, which will both increase success rate and reduce cost, and the cost of the facility where the procedure is carried out.

6.9 Literature review of economic evaluations

The five studies[19,20,26,33,39] identified in the review of existing economic evaluation are described below. A description of potentially useful costing studies[5,20,43] is also given below.

Martinez 2002[33]

Martinez 2002[33] was a randomised double blind study comparing diazepam with midazolam as a premedication administered in conjunction with meperidine prior to procedural sedation with propofol in children having upper endoscopy. It is considered to be a partial economic evaluation as the only costs reported were the costs of the study drugs themselves which was $25.95 for midazolam and $0.92 for diazepam. It is therefore not useful for decision making as it does not estimate the overall resource use and costs of the alternative sedation strategies. For example, it does not consider the cost of treating adverse events.

Iannalfi 2005[19]

Iannalfi 2005[19] was a randomised controlled trial comparing moderate sedation with general anaesthesia in children having lumbar puncture and/or bone marrow aspiration. It only enrolled 31 children and therefore there were less than 20 patients in each arm. RCTs with less than 20 patients in each arm are excluded from the clinical effectiveness reviews as the groups are not sufficiently large for randomisation to provide groups who are reliably comparable for known and unknown confounders. We have therefore not considered it any further as the clinical effectiveness outcomes are potentially open to bias.

Lee 2000[26] and Jameson 2007[20]

These two studies were model based cost minimisation studies which estimated the cost per patient treated and assumed that the health benefits would be equivalent[20,26]. In both cases the studies compare sedation with anaesthesia for patients undergoing dental treatment. After considering the clinical review evidence, the GDG agreed that it is not likely that the use of sedation techniques will lead to significant changes in quality-adjusted life years as changes in health-related quality of life will only occur over a short period of time. The GDG also suggested that the adverse events observed in the clinical review are not expected to lead to long-term effects that will result in significant QALY differences across different techniques. However, the results of these studies could not be used as the GDG wanted to compare four different sedation strategies with GA in children undergoing dental procedure.

Pershad 2006[39]

The final model based evaluation[39] used clinical evidence from RCT and non-RCT sources to compare four different procedural sedation and analgesia (PSA) techniques for use in children requiring manipulation of a forearm fracture in the emergency department (ED). The four techniques were:

- Deep sedation with ketamine / midazolam (K/M)
- Deep sedation with propofol / fentanyl (P/F)
- Deep sedation with fentanyl / midazolam (F/M)

- Axillary approach to brachial plexus regional block with midazolam premedication (ABRA/M)

The model incorporated evidence on adverse event rates, duration of sedation, and likelihood of PSA failure. The clinical effectiveness and adverse effects data were derived from published literature following a systematic literature search, but the methods for selecting papers has not been explicitly reported. Some additional data from an unpublished trial undertaken in the author's institution were also incorporated in the analysis. The methods described in the paper suggest that the estimates obtained from the RCTs were synthesised in a way which did not maintain randomisation. The adverse events considered in the model were emesis, recovery agitation, respiratory depression requiring assisted ventilation and lidocaine toxicity. It was assumed that deep sedation with P/F would be used when axillary block failed. It was assumed that deep sedation would be 100% successful for all three techniques based on existing data showing that success rates are between 98% and 100% with K/M and F/M.

Resource use included medication costs for sedation and analgesia techniques, staffing costs for administering sedation and treating adverse events, and ED overhead costs based on duration of ED stay which was assumed to vary according to the total sedation time. Duration of ED stay was used as the clinical effectiveness outcomes so that the cost-effectiveness was reported as the cost per hour of time in the ED avoided. Unit costs were reported for staff time, ED overheads and medication costs. Costs were calculated from the hospital's perspective and were reported in US$, but the price year was not reported. Uncertainty was examined deterministically using one-way and two way sensitivity analysis. A probabilistic sensitivity analysis was used to consider the importance of parameter uncertainty but the authors simply report that the model was "robust" through 1000 iterations.

P/F was found to be the dominant strategy as it had the lowest cost and the shortest ED stay which was the sole effectiveness outcome considered. However this conclusion was sensitive to several key assumptions. The conclusions would be different if the rate of respiratory depression for P/F were to increase from 1.1% to 6.9%, if the rate of lidocaine toxicity were to be reduced from 2.5% to less than 1%, or if the rate of failure of axillary block were to be reduced from 6.8% to less than 2%. Small increases (e.g 3 mins) in the duration of physician time required to administer deep sedation would result in axillary block being the lowest cost option, which is quite possible given that this duration was not well defined by the evidence base. This economic evaluation is considered to be only partially applicable as it is a US based study and the assumptions regarding resource use and unit costs that have been used to populate the model may not be relevant in a UK NHS setting. It is also not clear whether the PSA regimens compared are equivalent in terms of reducing pain and discomfort for patients or whether the main outcome measure, length of emergency department stay, is an important outcome for patients and their families and carers. It is considered to have potentially serious limitations due to uncertainty around the selection and synthesis of effectiveness data and the sensitivity of the conclusions to key assumptions regarding physician time.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author, Year: Pershad 2006[39] Country: US Funding: Not stated Type of analysis: Cost-effectiveness	Study design: Decision tree model Time horizon: Duration of emergency department stay Discounting: NA Perspective: Hospital Cost year: Not stated	Theoretical cohort or 10 year olds requiring manipulation of fractured forearm in the emergency department	1) Deep sedation with ketamine/midazolam 2) Deep sedation with fentanyl/midazolam 3) Deep sedation with propofol/fentanyl 4) Axillary Block/ midazolam	Effectiveness: Duration of emergency department stay Cost: Staff costs for clinical contact time plus overheads based on length of stay, medication costs ICER: cost per hour of stay avoided	1) 1.75 hours 2) 2.19 hours 3) 0.55 hours 4) 1.06 hours 1) US$ 105.32 2) US$ 159.79 3) US$ 84.06 4) US$ 88.18 Not relevant as 3) dominates all others	Sensitivity analysis shows that results are not robust to small changes in physician time required It is unclear whether the method of evidence synthesis for clinical effectiveness outcomes maintained randomisation

6.10 Costing studies

The review of costing studies was restricted to UK studies as costs are likely to vary significantly between different healthcare settings.

Blain 1998[5]

This costing study compares the cost of inhaled sedation (nitrous oxide in oxygen, titrated up to a maximum of 40%) with local anaesthesia to general anaesthesia (intravenous induction with inhalational maintenance) for children having dental extractions from a UK NHS perspective. Treatment was provided in a UK secondary care setting. The costing analysis was restricted to staffing costs during treatment and recovery. If treatment took place over more than one visit then the total duration over multiple visits was used. Staff costs were based on the agreed minimum staffing level for each service and 1994 salary scales. These were used to calculate the ratio of staff costs per minute during treatment and recovery for the two services and overall costs were reported using units that represent one minute of care within the sedation service (see Table 31 below). The duration of treatment and recovery was taken from a case-control study conducted in the UK which was also reported within Blain 1998[5]. Children who were not suitable for treatment with sedation were excluded from both the sedation and anaesthesia cohorts before 265 matched pairs (matched for age and gender) were selected. The mean age was 7.63 (SD 2.45) and 7.54 (SD 2.46) for the sedation and anaesthesia groups respectively. However, there were a much larger number of patients rejected from the sedation group (42% versus 16%) suggesting that the groups may not be comparable. The overall costs were 64.3 units for sedation and 80.8 units for anaesthesia. It is not possible to convert these back to UK£ from the data provided. This study is directly applicable as it takes a UK NHS perspective although its usefulness is limited as it does not report the actual costs and therefore these cannot be uplifted to reflect current prices. The duration of treatment and recovery are key factors in the costing analysis and these have potentially serious limitations as they are based on a case-control study, in which there were considerably more patients excluded from one group.

Table 31 Staffing levels, cost ratios and duration of treatment and recovery associated with sedation and general anaesthesia

	Sedation	General anaesthesia
Staffing levels during treatment	Registrar Dentist, Dental Nurse	Consultant Anaesthetist, Registrar Dentist, 2 x Dental Nurse
Staffing levels during recovery	Dental Nurse	Staff Nurse, Dental Nurse
Cost ratio during treatment	1	2.8
Cost ratio during recovery	1	2.2
Duration of treatment (minutes)	45.1	7.4
Duration of recovery (minutes)	19.2	27.3
Total costs (units)	64.3	80.8

Shaw 1996[43]

This was a prospective study that evaluated treatment success, assessed parents' and children's satisfaction, and compared the cost of inhalation sedation with that of existing general anaesthesia. It was carried out in children having dental extractions or minor oral surgery in a UK NHS secondary care setting. Treatment was judged as successful by the clinician if the procedure was completed. Data on treatment satisfaction was collected by questionnaire. Cost was based on hospital data and included staff cost only. It excluded the cost of other hospital overheads, such as the equipment, anaesthetic gases and reception staff. Ninety percent of children treated with sedation completed treatment. Thirteen children were treated with general anaesthesia. The cost per patient of providing treatment with sedation was reported to be 30% less than that for outpatient general anaesthesia and 57% less than day-stay general anaesthesia. More detailed cost information was not reported. This study has a number of limitations and should be cautiously interpreted. The number of patients studied for general anaesthesia was small. Cost data included only staff cost and this was not reported in enough details to allow judgement on quality. The study sample was not randomised. There were no sensitivity analyses on the results.

Jameson 2007[20]

This paper compares the cost of providing advanced conscious sedation in a primary care-based service with the cost of treatment under a dental general anaesthetic (DGA) in a hospital based community dental service. The cost analysis for advanced conscious sedation takes into account the rate of referrals for DGA after initial assessment and the rate of sedation failure, which are estimated from 2,771 patient records. The rate of failure under DGA is not considered and is therefore assumed to be 100%.

The cost of treatment under DGA is presented using both NHS reference costs[12] and a bottom-up costing using local audit data. The bottom-up costing included salary costs for anaesthetists, dental staff and administration staff and the cost of consumables, equipment, portering and the availability of inpatient beds reserved for use by the service. Separate costs were estimated for long and short procedures and an average cost was derived using weighting list data to estimate the ratio of long to short procedures. Using the HRG costs, the cost for short and long procedures was £568 and £616 respectively, with a mean cost of £590.21. The average cost estimate based on the local audit data was much lower at £359.91.

The cost of treatment under sedation was estimated using the patient list data from 205 patients and applying the relevant fees paid to the primary care based sedation service by the NHS, giving a cost per patient of £223.78. Once the additional cost of referring patients who had failed under sedation for a DGA are included, the cost is £245.57 per patient treated.

Sensitivity analyses were conducted on the rate of sedation failures, the rate of referrals for DGA following sedation failure and the rate of referrals for DGA following assessment. The rate of failure would need to increase to 77% before DGA became the lowest cost option, whilst the rate of referral following failure was not found to be a significant factor. If the rate of referrals following assessment at the sedation service were to increase to above 36.32% then DGA would be the lowest cost option, however the current rate is only 4-5%.

It is not clear whether the patients receiving care under the two services are similar. It is not known whether the age profile of the two cohorts was similar or how many patients receiving DGA had special needs meaning that they would not be able to receive treatment in a primary care setting. The fact that 56.7% of those failing under sedation (1.98% of all those receiving sedation) were referred back to their GP as there was insufficient justification for a DGA suggests that the cohorts may not be comparable. This study is considered to have minor limitations as there is uncertainty regarding the comparability of the cohorts being treated in the different settings, but the sensitivity analyses suggest that the conclusions are unlikely to be affected by small differences in the case mix. The results are considered to be directly applicable to the UK NHS dental services as a whole with the caveat that there would need to be sufficient demand within a particular region to meet the upfront costs of establishing a primary care based sedation service such as this as an alternative to DGA.

Table 32 Excluded studies and reasons for exclusion

Author, year	Reason for exclusion from cost-effectiveness review
Blain 1998*[5]	Excluded as non-RCT design for outcomes
Bluemke 2000[6]	Excluded as non-RCT design for outcomes
DeLoach 2005[11]	Excluded as non-RCT design for outcomes
Foglia 2004[15]	Excluded as non-RCT design for outcomes
Harned 2001[17]	Excluded as non-RCT design for outcomes
Jameson 2007*[20]	Excluded as equivalence assumed but not demonstrated
Kezerashvili 2008[21]	Excluded as non-RCT design for outcomes
Lalwani 2007[24]	Excluded as non-RCT design for outcomes
Lawrence 1998[25]	Excluded as non-RCT design for outcomes
Lee 2000[26]	Excluded as equivalence assumed but not demonstrated
Movaghar 2000[35]	Excluded as non-RCT design for outcomes
Nelson 2000[36]	Excluded as non-RCT design for outcomes
Squires 1995[44]	Excluded as non-RCT design for outcomes
Yen 2008[51]	Excluded as age 16+ and high mean age, 49+-22 and 46+-19)
Westrup 2007[45]	Excluded as comparison not relevant
Loewy 2006[28]	Excluded as no cost data
De Amorim E Silva 2006[9]	Excluded as no cost data
Mamede 2008[30]	Excluded due to age range (16-72, mean 47.5)
Adams 2007[2]	Excluded as no cost data
Khan 2007[22]	Excluded as no cost data
Shaw 1996*[43]	Excluded as non-comparative study
Iannalfi 2005[19]	Excluded as RCT with N<20 in each arm
Martinez 2002[33]	Excluded as cost data limited to drug costs only

* Relevant UK costing studies.

6.11 Reference List (for Appendix F, Cost-effectiveness analysis)

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7 Appendix G - Recommendations for research

7.1 Recommendation for research on pre-sedation assessment

PICO question	For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques, what factors are needed to develop a tool, or what tools should be used to standardise assessment and/or monitoring, in establishing the need for sedation and in reducing the potential risk of adverse events? *Question*: What factors determine the need for sedation? *Population*: Children requiring sedation for procedures *Intervention*: Assessment of factors that could determine whether sedation is the best choice for the patient. Development of an assessment tool. Application of the assessment tool to predict whether sedation is an effective and safe option for patients undergoing procedures. *Comparison*: Children assessed versus not assessed by an "Assessment tool" *Outcome*: Quality of care (patient/carer/ healthcare professional feedback) and incidence of complications of sedation.
Importance to patients or the population	Patients want to receive the best care. Healthcare professionals may need a tool to help them advise patients/carers on the best choice of technique for a procedure. If sedation is ineffective the patient will have to be anaesthetised later – perhaps the

	following day or in another hospital.
Relevance to NICE	There is variation on practice across the NHS.
Relevance to the NHS	NHS resources could be used more effectively if patients were managed with effective techniques. Sedation failure is expensive. Anaesthesia is always effective but is expensive and limited resource.
National priorities	Making correct choices for the type of sedation/anaesthesia proposed should reduce costs.
Current evidence base	There are no published assessment tools for sedation
Study design	Observational study to determine the important factors. Consensus study to develop a tool Randomised comparison of children assessed versus not assessed using the tool.
Feasibility	Large teaching hospitals have many patient who need procedures under sedation.
Other comments	Funding is needed for a research worker to develop the assessment tool and to coordinate the consensus and assessment studies. This person could work alongside workers mentioned in the other priority research projects.
Importance	Developing an assessment tool should improve quality of care.

7.2 Recommendation for research on training for personnel involved in sedation

PICO question	For personnel involved in delivering sedation to children and young people under the age of 19 undergoing diagnostic and therapeutic procedures what training is required to both achieve and maintain essential skills? Question: Does airway training using a manikin improve airway skills required for safe sedation practice? *Population*: Healthcare professionals training to deliver sedation *Intervention*: Airway training using a manikin in addition to standard airway training on anaesthetised patients. Two intervention groups: (1) manikin training every 3 months, and (2) manikin training every month. C*omparison*: Standard airway training on anaesthetised patients (no manikin training) O*utcome*: Time taken to achieve successful management of airway problems in anaesthetised patients
Importance to patients or the population	Airway problems in sedated patients should be infrequent. Consequently, when they do occur healthcare professionals' airway skills may be slow and patients may be at risk of hypoxia. Healthcare professional administering sedation have standard airway training but this may not be sufficient. Special airway training may be necessary.
Relevance to NICE	Currently there is much variation in airway skills in healthcare professional who deliver sedation. Training in airway skills needs to be developed and proven to be effective. Once established, airway training should be undertaken by all sedationists so that, across the NHS, there is a high standard of managing airway problems.
Relevance to the NHS	Safe airway management should improve patient safety. Airway training should improve flexibility of working for healthcare professional because any member to the team, whichever professional group, can achieve airway skills.
National priorities	Patient safety. Delivery of high standard of care within current staffing resources
Current evidence base	Training on manikins can improve performance. Airway training for sedation in children and young people has not

	been developed.
Study design	Randomized controlled comparison of three methods of training airway skills. Assessment of skills will be by a "single blind" independent assessor.
Feasibility	Trainee and established healthcare professionals (doctors, dentists and nurses) are available in large teaching hospitals. These hospitals should benefit from having effective airway training.
Other comments	Manikins are available in most teaching institutions however funding maybe required for new manikins. Funding will be required for a study coordinator.
Importance	Airway training is an essential skill in many areas of healthcare delivery.

7.3 Recommendation for research on drugs combination

PICO question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, what drugs can be combined with midazolam to achieve sedation (at mild, moderate, and deep levels) with low risk of loss of consciousness for sedation in different settings? Question: What dose of fentanyl can be combined with midazolam for effective and safe sedation in children and young people? *Population*: Children undergoing painful procedures in Emergency Department setting *Intervention*: fentanyl *Comparison*: three doses of fentanyl *Outcome*: observation score of distress during procedure. Incidence and severity of complications
Importance to patients or the population	Many patients require moderate sedation for painful procedures in the Emergency Department setting. A sedation technique is needed that can be applied across a wide range of painful procedures
Relevance to NICE	There is wide variation of standards of sedation practice across the NHS
Relevance to the NHS	Healthcare professionals need guidance on the safe doses of common drugs in children
National priorities	Midazolam and fentanyl are widely used sedation drugs yet little data are available to inform on the effective and safe doses for moderate sedation
Current evidence base	Dose finding studies have not been carried out in children for this combination of drugs
Study design	Randomised double blind comparison of three doses of fentanyl combined with midazolam (dose compatible with moderate sedation)

Feasibility	Sufficient numbers of children requiring sedation may not be available in a single Emergency Department. The study would therefore need to be multi-centre
Other comments	Funding would be required for coordinators of this study. These people could work alongside workers mentioned in the other priority research projects.
Importance	The combination of midazolam and fentanyl could be useful across a wide range of situations involving sedation for painful procedures

7.4 Recommendation for development of a national registry of sedation

PICO question	Establishment of a national registry for paediatric sedation, to provide a database with sufficient power to give more useful data on safety and efficacy Question: What are the safety and efficacy profiles of sedation techniques in current practice? *Population*: Children and young people undergoing sedation in selected hospitals in the UK *Intervention*: Observational audit of clinical practice. Self completed reporting. *Comparison*: N/A *Outcome*: Incidence of complications and quality of patient experience.
Importance to patients or the population	Patients and healthcare professionals need to know the safety and efficacy profile of current sedation practice
Relevance to NICE	There is variation in standards of practice. A national data base could aid implementation of NICE guidance
Relevance to the NHS	Safety data on sedation is important to the service
National priorities	Safety is a high priority
Current evidence base	Safety data from a large sample of patient are not available in the UK
Study design	Large scale audit program of practice
Feasibility	Involving all hospitals will be difficult. Selecting paediatric hospitals who have a large sedation practice and who want to take

	part should be feasible
Other comments	Funding will be necessary to employ a coordinator of this audit project. This person could work alongside workers mentioned in the other priority research projects.
importance	Planning services of children depends upon accurate estimation of demand, quality and safety. Data on sedation will help planning, training and implementation of sedation services

8 Appendix H-Review protocol form

8.1 Objective

To determine the effectiveness of sedation for children and young people (under the age of 19 years).

8.2 Definition of sedation

Sedation is a technique which involves the depression of consciousness by drugs. The aim of sedation during diagnostic or therapeutic procedures includes reducing fear and anxiety, and minimising movement. The importance of each of these aims will vary depending on the nature of the procedure and the characteristics of the patient. For example, in younger children sedation may be necessary to ensure that movement is minimised during non-painful procedures such as a magnetic resonance imaging (MRI) scanning; in older children sedation may be necessary to minimise the physical and psychological consequences of a painful procedure such as a lumbar puncture.

8.3 Selection criteria for intervention reviews

Studies will be included if they meet the following selection criteria:

1. Types of studies

- randomised trials (RCTs)
- quasi-randomised studies (e.g. allocation by alternation, date of birth, etc)
- other study designs will be considered in discussion with GDG if RCTs are not found
- in accordance with NICE methods, studies will be restricted to the English language (unless recommended otherwise by the GDG)
- studies with fewer than 20 patients in each arm will not be considered

- studies in indirect populations will be considered if there are none in direct populations (e.g. adults)

2. Healthcare settings

- Hospital settings, including inpatients, outpatients, radiology and emergency departments
- Primary care, including dental and medical general practice

3. Types of participants

Included

Infants, children and young people under the age of 19 who are receiving sedation by any technique for diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.

Excluded

- Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
    - sedation for critically ill patients requiring mechanical ventilation
    - sedation in palliative care
    - sedation in the treatment of mental health conditions
    - sedation given as premedication for general anaesthesia or as postoperative analgesia
    - night sedation
- Patients having diagnostic or therapeutic procedures under general anaesthesia

4. Types of interventions

The following pharmacological interventions, described in the children's BNF, will be included. Individual drugs will be considered separately and in combination. A class effect is not assumed.

- Drug class: Benzodiazepines; drugs: Midazolam
- Drug class: Inhalational anaesthetics; drug: Nitrous oxide
- Drug class: IV anaesthetics; drugs: Ketamine (painful procedures) and Propofol
- Drug class: Choral and derivatives; drugs: Chloral hydrate and Triclofos sodium (painless procedures)

- Drug class: Opioids; drugs: Morphine, Pethidine (Merperidine), Fentanyl, Alfentanil, Remifentanyl

- Drug class: Inhalation anaesthetics; drugs Sevoflurane and Isoflurane

Combinations of drugs

Any combination will be considered.

All doses will be included. We will also record how the authors determined the dose that is needed to achieve the desired level of cooperation and/or anxiolysis.

For all sedative agents except ketamine and opioids, any route of administration will be considered including buccal, oral, intravenous, inhalation, rectal, intramuscular, transmucosal. Bolus and titrated doses will be included. Ketamine will be considered when given by intramuscular and intravenous routes. For opioids, fentanyl and morphine will be considered when administered by intravenous routes and diamorphine when administered by intranasal route.

Techniques of administration including patient control, operator control and control by a separate sedationist will be considered. Interventions will be included regardless of who administered them and this will be noted, e.g. nurses, anaesthetist, trained sedationist.

The guideline will not review non-pharmacological treatments alone for diagnostic or therapeutic procedures because these are not sedation by definition. However, combinations of sedation with non-pharmacological treatments will be compared with non-pharmacological treatment alone, i.e. investigating adjunctive effects of sedation.

Any non-pharmacological intervention will be included as part of the combination treatment, provided it is a definite intervention, as distinct from usual care.

5. Types of comparisons

The following comparisons will be included.

- intervention (including combinations) versus no intervention or placebo or usual care

- intervention A versus B

- intervention A + B versus B

- pharmacological versus non-pharmacological

- pharmacological + non-pharmacological versus non-pharmacological

- pharmacological + analgesia versus analgesia

- pharmacological versus general anaesthesia

- dose A versus dose B
- duration 1 versus duration 2
- route of administration 1 versus 2

6. Types of outcome measures

The following outcomes will be considered.

Primary outcome:

- Successful completion of diagnostic or therapeutic procedure
    - measured as the number of patients for whom the diagnostic or therapeutic procedure was carried out and completed.

Secondary outcomes:

- Behavioural ratings including:
    - pain as assessed by the patient or parent or other observer using validated pain scales e.g. Visual Analogue Scale (VAS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), FACE,.
    - procedural distress and/or anxiety as assessed by the patient or parent or other observer using validated scales e.g. Visual Analogue Scale (VAS), Observation Scale of Behavioral Distress (OSBD).
    - patient or parent satisfaction including preference
- Sedation timing including
    - length of induction: time from administration of sedation drug to initiation of procedure
    - duration of procedure
    - length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
    - total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Adverse events:

- Aspiration
- Respiratory intervention, including:
    - oral-pharyngeal airway

- endotracheal intubation
- assisted ventilation

- Cardiac arrest requiring either/or:
  - external cardiac massage
  - defibrillation
- Oxygen desaturation <90%
- Vomiting

APPRAISAL OF METHODOLOGICAL QUALITY

The methodological quality of each study will be assessed by one reviewer and randomly checked by a second. Quality items will also be assessed by type of study. For randomised trials, the following factors will be considered in assessing the potential for bias:

1. *A priori* sample size calculation:
   - whether or not this was carried out
2. Method of generation of the randomisation sequence:
   - the means by which interventions are distributed amongst the participants
   - whether the method was reported or unclear (i.e. no details given)
   - whether the reported method was adequate, inadequate or partial (Table 1)
3. Allocation concealment at randomisation:
   - the means of preventing the treatment assignment being known before the time of allocation
   - whether the method was reported or unclear (no details)
   - whether the reported method was adequate, inadequate or partial (Table 1)
4. Baseline comparability of treatment groups
   - Age, procedure for which sedation is required, mental state, anxiety state, disease state, fasting state
5. Patients stated to be blinded
6. Outcome assessor stated to be blinded
7. No loss to follow up for each outcome:
   - studies with at least 20% of data missing from any group were considered to be potentially biased, more so if there was differential drop out from any one group or if the missing data was known to be significantly different from the remaining data

- those with moderate loss to follow up (20 to 50%) were considered in sensitivity analyses
- those with 50% or more patients missing from any one group were regarded as flawed and not analysed further

8. Intention to treat analysis:
   - Trial participants should be analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities and
   - all participants should be included regardless of whether their outcomes were actually collected

METHODS OF THE REVIEW

Data synthesis

Meta-analysis of similar trials, where appropriate, will be carried out using The Cochrane Collaboration's analysis software, Review Manager (Version 5). Trials will be pooled using a fixed effects model and plotted on forest plots. Where there is significant heterogeneity, a random effects model will be used as a sensitivity analysis.

Crossover trials will be treated separately from parallel trials unless there is sufficient data to allow their combination. First period only results will be treated with caution.

For dichotomous studies, intention to treat analyses will be used (including all participants according to their assigned groups) where reported by the study authors, and failing that, available case analyses (all those reporting an outcome) as reported by the authors will be used. Where there are incomplete data reported (more than 20% missing in any one group), sensitivity analyses will be carried out, excluding these studies.

Where it is possible to combine studies, outcomes will be summarised for dichotomous data using relative risks or Peto odds ratios (where there are studies with no events in one arm). Numbers needed to treat, with their 95% confidence intervals and the control group rate (range of rates) to which they apply, will be calculated from the risk difference where appropriate. The number needed to treat (NNT) is the number of patients who would have to be treated for one to have an improved outcome.

For continuous data, weighted mean differences will be used and where the studies have different scales, standardised mean differences will be used. Studies reporting final values or change scores will be combined if the scales used are the same across studies, otherwise they will be reported separately. If both final values and change scores are reported, the former will be used. Summary statistics and their 95% confidence intervals (95% CI) will be reported where sufficient detail allows their calculation, together with the control group range.

We will assess heterogeneity between trials by visual inspection of forest plots, noting where there is poor overlap of horizontal lines, and by using statistical measures: the χ^2 test for heterogeneity and the level of inconsistency, I^2 ($I^2 = [(\chi^2 - df)/ \chi^2] \times 100\%$, where df is the degrees of freedom). We will consider that there is heterogeneity if the heterogeneity p-value is less than 0.1 and/or I^2 is greater than 50%. Any heterogeneity

will be explored further and unexplained heterogeneous results will not used as the basis for recommendations.

Stratification

Studies will be stratified by:

- weight: all babies with weight of less than 5 kg will be considered separately
- route of administration
- type of procedure: painful and non-painful; repetitive procedures will not be treated separately

Combining studies

Studies will be combined regardless of:

- dose
- duration of intervention
- procedure (within painful and non-painful groups)
- setting (e.g. dentistry, A&E etc)
- age

Subgroup analyses

The following subgroups will be considered if there is heterogeneity:

9. Drug dose
10. Age groups
    - 1 year and below
    - 1-5 years
    - 5-12 years
    - over12 years (physiologically similar to adults)
11. Population/patient type:
    - special needs and non-special needs, e.g. physical and learning disabilities
12. sedation level using ASA grading:
    - Minimal: formerly anxiolysis
    - Moderate (conscious sedation)
    - Deep
13. route of delivery of sedation (bolus/titration):
14. ASA classification (Appendix II)
    - ASA I and II versus ASA III to V

15. Procedure
16. who administered sedation technique(s)

Review Protocol – Fasting

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques should fasting versus no fasting be implemented to prevent adverse outcomes?
Objectives	To establish whether the patient should be fasted and for how long before the procedure under sedation to minimize adverse events.
Population	<u>Included (for the search strategy 1 only):</u> Infants, children and young people under the age of 19 who are receiving sedation by any technique for diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia. <u>Excluded (for the search strategy 1 only)</u>: Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including: • sedation in critically ill patients requiring mechanical ventilation • sedation in palliative care • sedation in the treatment of mental health conditions • sedation given as premedication for general anaesthesia or as postoperative analgesia • night sedation. <u>Included (for the search strategy 2 only)</u>: Healthy children and young people ASA I-II who were undergoing elective surgery under general anaesthesia <u>Excluded (for the search strategy 2 only)</u>: Children and young people with gastrointestinal disease
Intervention	• Fasting before general anaesthesia • Fasting before sedation with one of the following drugs: midazolam, ketamine, propofol, chloral hydrate, nitrous oxide, sevoflurane, fentanyl IV, morphine IV or diamorphine IN
Comparison	Fasting versus no fasting
Outcomes	Outcomes for adverse events as evidenced by: • Aspiration • Respiratory intervention, including: – oral-pharyngeal airway – endotracheal intubation – assisted ventilation • Cardiac arrest requiring either/or: – external cardiac massage – defibrillation • Oxygen desaturation <90% • Vomiting

Search strategy

1) A full search of the literature relevant to fasting for paediatric sedation was conducted. The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted by study design to RCTs and non RCT observational studies.

2) To update the RCN guideline on fasting[1] a literature search was conducted for perioperative fasting in children. The databases searched were Medline (from 2004 to Jan 18th 2010), Embase (from 2004 to Jan 18th 2010), The Cochrane Library (2004 to 2009 Issue 4) and CINAHL (from 2004 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted by study design to RCTs and non RCT observational studies.

The review strategy

The review for this question consisted of three evaluation processes:

1) The RCN guideline Perioperative fasting in adults and children, 2005[1] was assessed using the Agree Instrument for appraisal of clinical guidelines.

2) An update search was conducted for perioperative fasting in children and young people from 2004 to 2009, using key words 'anaesthesia,' 'fasting,' and 'children.' The purpose of this search to was identify recent publications which might impact recommendations in the RCN guideline Perioperative fasting in adults and children, 2005[1].

3) A full search of the literature relevant to fasting for sedation in children and young people, using key words 'sedation,' 'fasting,' and 'children' was conducted.

One RCT met inclusion criteria. Six observational studies were also included in this review, due to lack of further RCT data.

Review Protocol – Psychological Preparation

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques what standard psychological preparation, coping skills and strategies should be used?
Objectives	To provide advice on psychological techniques for an effective patient management.

Population	Included:
	Infants, children and young people under the age of 19 who are receiving sedation by any technique for diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Psychological preparation pre-sedation
Comparison	• No intervention, usual care • Pre-medication with drug therapy • Another non-pharmacological treatment

Outcomes	Outcomes for efficacy of psychological preparation:
	1. Completion of procedure
	2. Behavioural ratings including:
	  a. Pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI).
	  b. procedural distress as assessed by validated scales such as OSBD
	  c. Parent/patient satisfaction
	3. Sedation timing including
	  a. Length of induction (defined as time from administration of sedation drug to initiation of procedure)
	  b. Length of recovery (defined as time from completion of procedure to recovery criteria being met)
	The search for psychological preparation for paediatric sedation included both quantitative and qualitative literature. Only two RCTs were identified and therefore the review for this intervention was primarily a narrative review of observational studies and randomized controlled clinical trials conducted in other relevant contexts i.e., induction for anaesthesia and medical procedures

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design and included general anaesthesia literature.

The review strategy

Meta-analyses of *RCTs* will be conducted where possible and that if there is heterogeneity subgroup analysis will be conducted as appropriate

Review Protocol – Validated tools

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques, what validated tools should be used to support assessment?
Objectives	To establish what validated tools should be used to support clinicians to assess and decide whether the child: • should receive sedation OR • have general anaesthesia OR • have some other kind of pain/anxiety management • Note: this is not about measuring how deep a child is sedated
Population	Included: Infants, children and young people under the age of 19 who are receiving sedation by any technique for diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia. Excluded: o Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including: o sedation in critically ill patients requiring mechanical ventilation o sedation in palliative care o sedation in the treatment of mental health conditions o sedation given as premedication for general anaesthesia or as postoperative analgesia o night sedation. o Patients having diagnostic or therapeutic procedures under general anaesthesia.
Intervention	Validated instrument/tools/equations/algorithms
Comparison	Standard care or head-to-head comparison with another validated instrument/tools/equations/algorithms
Outcomes	Outcomes for efficacy for sedation sparing: 1. Completion of procedure
Search strategy	The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010). Studies were restricted to English language only. Searches were restricted using study design filters for RCTs, systematic reviews and observational studies

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – Midazolam (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is midazolam (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of midazolam.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for efficacy of midazolam:
	1. Completion of procedure
	2. Behavioural ratings including:
	  a. pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI).
	  b. procedural distress as assessed by validated scales such as

OSBD
   c. parent/patient satisfaction
3. Sedation timing including
   a. length of induction: time from administration of sedation drug to initiation of procedure
   b. duration of procedure
   c. length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
   d. total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – Midazolam (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is midazolam (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of midazolam.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for safety of midazolam::
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE. The methods of reviewing are detailed in Chapter 2.

Review Protocol – Ketamine (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is ketamine (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of ketamine.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	**Primary outcome:** Successful completion of diagnostic or therapeutic procedure measured as the number of patients for whom the diagnostic or therapeutic procedure was carried out and completed. **Secondary outcomes:** • complications – respiratory support • pain as assessed by the patient or parent or other observer

- distress/anxiety as assessed by the patient or parent or other observer
- patient or parent satisfaction, including preference
- length of stay or time to recover to pre-sedation state (includes prolonged drowsiness)

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy was based on RCT evidence only. Study details, methodology and results were extracted into an Access database. Further statistical analysis and meta analysis was carried out in Rev Man as required. An evidence profile and quality assessment was then entered into GRADE.

Review Protocol – Ketamine (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is ketamine (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of ketamine.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	**Adverse events:**
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety was based upon both RCT and non RCT observational evidence. Study details and results were extracted into tables for review by the GDG. Rates of adverse events were calculated as required.

Review Protocol – Chloral Hydrate (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is chloral hydrate (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of chloral hydrate.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	**Primary outcome:** Successful completion of diagnostic or therapeutic procedure measured as the number of patients for whom the diagnostic or therapeutic procedure was carried out and completed. **Secondary outcomes:** • complications – respiratory support

- pain as assessed by the patient or parent or other observer
- distress/anxiety as assessed by the patient or parent or other observer
- patient or parent satisfaction, including preference
- length of stay or time to recover to pre-sedation state (includes prolonged drowsiness)

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy was based on RCT evidence only. Study details, methodology and results were extracted into an Access database. Further statistical analysis and meta analysis was carried out in Rev Man as required. An evidence profile and quality assessment was then entered into GRADE.

Review Protocol – Chloral Hydrate (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is chloral hydrate (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of chloral hydrate.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	**Adverse events:**
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety was based upon both RCT and non RCT observational evidence. Study details and results were extracted into tables for review by the GDG. Rates of adverse events were calculated as required.

Review Protocol – Nitrous Oxide (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is Nitrous Oxide (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of Nitrous Oxide.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	**Primary outcome:** Successful completion of diagnostic or therapeutic procedure measured as the number of patients for whom the diagnostic or therapeutic procedure was carried out and completed. **Secondary outcomes:** • complications – respiratory support

- pain as assessed by the patient or parent or other observer
- distress/anxiety as assessed by the patient or parent or other observer
- patient or parent satisfaction, including preference
- length of stay or time to recover to pre-sedation state (includes prolonged drowsiness)

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy was based on RCT evidence only. Study details, methodology and results were extracted into an Access database. Further statistical analysis and meta analysis was carried out in Rev Man as required. An evidence profile and quality assessment was then entered into GRADE.

Review Protocol – Nitrous Oxide (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is Nitrous Oxide (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of Nitrous Oxide.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	**Adverse events:**
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety was based upon both RCT and non RCT observational evidence. Study details and results were extracted into tables for review by the GDG. Rates of adverse events were calculated as required.

Review Protocol – Opioids (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, are opioids (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of opioids.
Population	Included: Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia. Excluded: • Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including: o sedation in critically ill patients requiring mechanical ventilation o sedation in palliative care o sedation in the treatment of mental health conditions o sedation given as premedication for general anaesthesia or as postoperative analgesia o night sedation. • Patients having diagnostic or therapeutic procedures under general anaesthesia.
Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	Outcomes for efficacy of opioids: 4. Completion of procedure 5. Behavioural ratings including: d. pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI). e. procedural distress as assessed by validated scales such as

OSBD
   f. parent/patient satisfaction
6. Sedation timing including
   a. length of induction: time from administration of sedation drug to initiation of procedure
   b. duration of procedure
   c. length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
   d. total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – Opioids (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, are opioids (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of opioids.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for safety of opioids:
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE.The methods of reviewing are detailed in Chapter 2.

Review Protocol – Propofol (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is propofol (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of propofol.
Population	Included: Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia. Excluded: • Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including: o sedation in critically ill patients requiring mechanical ventilation o sedation in palliative care o sedation in the treatment of mental health conditions o sedation given as premedication for general anaesthesia or as postoperative analgesia o night sedation. • Patients having diagnostic or therapeutic procedures under general anaesthesia.
Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	Outcomes for efficacy of propofol: 7. Completion of procedure 8. Behavioural ratings including: g. pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI). h. procedural distress as assessed by validated scales such as

OSBD

i. parent/patient satisfaction

9. Sedation timing including
   a. length of induction: time from administration of sedation drug to initiation of procedure
   b. duration of procedure
   c. length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
   d. total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – Propofol (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is propofol (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of propofol.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for safety of propofol:
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE.The methods of reviewing are detailed in Chapter 2.

Review Protocol – Sevoflurane (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is sevoflurane (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of sevoflurane.
Population	Included: Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia. Excluded: • Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including: o sedation in critically ill patients requiring mechanical ventilation o sedation in palliative care o sedation in the treatment of mental health conditions o sedation given as premedication for general anaesthesia or as postoperative analgesia o night sedation. • Patients having diagnostic or therapeutic procedures under general anaesthesia.
Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	Outcomes for efficacy of sevoflurane: 10. Completion of procedure 11. Behavioural ratings including: i. pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI).

k. procedural distress as assessed by validated scales such as OSBD
l. parent/patient satisfaction

12. Sedation timing including
    a. length of induction: time from administration of sedation drug to initiation of procedure
    b. duration of procedure
    c. length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
    d. total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – Sevoflurane (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is sevoflurane (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of sevoflurane.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for safety of sevoflurane:
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE.The methods of reviewing are detailed in Chapter 2.

Review Protocol – Triclofos Sodium (efficacy)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is triclofos sodium (with or without: analgesia, another drug or psychological techniques) effective for sedation (at minimal, moderate, and deep levels) in comparison with usual care, with analgesia alone, with another sedation drug, with psychological techniques or with general anaesthesia?
Objectives	To estimate the effectiveness of triclofos sodium.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2
Outcomes	Outcomes for efficacy of triclofos sodium: 1. Completion of procedure 2. Behavioural ratings including: m. pain as assessed using validated pain scales such as FACE, VAS, CHEOPS, Spielberger State-Train Anxiety Inventory (STAI).

n. procedural distress as assessed by validated scales such as OSBD
o. parent/patient satisfaction

3. Sedation timing including
   a. length of induction: time from administration of sedation drug to initiation of procedure
   b. duration of procedure
   c. length of recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state (includes prolonged drowsiness)
   d. total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were restricted using study design filters for RCTs and systematic reviews.

The review strategy

The review for drug efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. The methods of reviewing are detailed in Chapter 2. An evidence profile and quality assessment will be then entered into GRADE.

Review Protocol – triclofos sodium (safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is triclofos sodium (with or without: analgesia, another drug or psychological techniques) safe for sedation (at mild, moderate, and deep levels) in different settings?
Objectives	To estimate the safety of triclofos sodium.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures.
Comparison	The following comparisons will be included. • intervention (including combinations) versus no intervention or placebo or usual care • intervention A versus B • intervention A + B versus B • pharmacological versus non-pharmacological • pharmacological + non-pharmacological versus non-pharmacological • pharmacological + analgesia versus analgesia • pharmacological versus general anaesthesia • dose A versus dose B • duration 1 versus duration 2 • route of administration 1 versus 2

Outcomes	Outcomes for safety of triclofos sodium:
	• Aspiration
	• Respiratory intervention, including:
	  ○ oral-pharyngeal airway
	  ○ endotracheal intubation
	  ○ assisted ventilation
	• Cardiac arrest requiring either/or:
	  ○ external cardiac massage

    - defibrillation
- Oxygen desaturation <90%
- Vomiting

Search strategy

The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010).

Studies were restricted to English language only.

Searches were not restricted by study design.

The review strategy

The review for drug safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE.The methods of reviewing are detailed in Chapter 2.

Review Protocol – Sedation sparing (efficacy and safety)

Component	Description
Review question	For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, does a combination of psychological techniques and sedation drugs lead to sedation sparing?
Objectives	To establish whether non-pharmacological intervention(s) reduce the amount of the sedative agent required and used in each arm.

Population	Included:
	Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures including dental surgery and minor operations carried out under local anaesthesia.
	Excluded:
	• Patients requiring sedation for purposes other than for diagnostic or therapeutic procedures including:
	  ○ sedation in critically ill patients requiring mechanical ventilation
	  ○ sedation in palliative care
	  ○ sedation in the treatment of mental health conditions
	  ○ sedation given as premedication for general anaesthesia or as postoperative analgesia
	  ○ night sedation.
	• Patients having diagnostic or therapeutic procedures under general anaesthesia.

Intervention	Sedation for diagnostic or therapeutic procedures
Comparison	The following comparisons will be included. • pharmachological + non-pharmacological versus pharmacological
Outcomes	Outcomes for efficacy and safety as detailed in outcomes section of this chapter and the following additional outcome(s) for sedation sparing: 1. volume (dose) of the sedation agent used in each arm
Search strategy	The databases searched were Medline (from 1950 to Jan 18th 2010), Embase (from 1980 to Jan 18th 2010), The Cochrane Library (all dates available to 2009 Issue 4) and CINAHL (from 1982 to Jan 18th 2010). Studies were restricted to English language only. Searches were not restricted by study design.
The review strategy	The methods of reviewing are detailed in Chapter 2.. The review for efficacy will be based on RCT evidence only. Study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. T An evidence profile and quality

assessment will be then entered into GRADE.

The review for safety will be based upon both RCT and non-RCT observational evidence. For RCT evidence, study details, methodology and results will be extracted into an Access database. Further statistical analysis and meta analysis will be conducted where possible and carried out in Rev Man as required. For non-RCT observational evidence, study details and results will be extracted into tables and rates of adverse events will be calculated as required. All evidence will be reviewed by the GDG. An evidence profile and quality assessment will be then entered into GRADE.

9 Appendix I - AGREE Tool

See separate file

10 Appendix J – Licensing indications

See separate file.