Sedation in children and young people

Foreword

Advances in medicine over the last 20 years have increased the demand for invasive investigations and procedures. The type of procedure can range from painless imaging that requires immobility to painful or uncomfortable minor surgery. Whereas adults can cope with these procedures, children often need more than simple reassurance and pain relief; they need either sedation or anaesthesia. The problem with sedation is its unpredictability. If managed well, it can be effective but sometimes it is not effective enough unless the doses are increased and this risks causing unconsciousness and suppression of vital protective reflexes leading to potentially dangerous hypoxia. If however, sedation is inadequate, the distress can be remembered for a lifetime and make any subsequent procedure much more difficult. There is a dilemma therefore between giving too much and too little. Anaesthesia, in comparison, is reliable but involves specialist skills and facilities, and may not always be an appropriate use of resources.

There is evidence that large numbers of children in the UK undergo single or repeated procedures and the perception is that there is considerable variation in the services that are provided. The common question asked is “What drugs are safe and effective?” and the Scottish Guideline Network guideline published in 2007 reviewed the evidence and drew useful conclusions. However, at the stakeholder meeting at the inception of this NICE guideline a different concern was raised – “Healthcare practitioners need to be trained to use sedation safely”. In other words, it became clear that the problem was less “What drugs?” but more “Who can administer them?”. Indeed, if it can be agreed that a chosen drug technique is effective, people need to know who can use it safely.

In consequence we have had two broad aims. Our first was to review the evidence of efficacy and safety of common drug techniques, and our second was to form a consensus view on what resources are necessary. This included not only the facilities, the equipment and the staff, but also the training of staff to ensure that they have adequate knowledge, skills and judgment.

Our Guideline Development Group (GDG) included doctors, nurses, dentists, radiographers, anaesthetists and a psychologist, as well as the public, who were all expert and experienced in working with children. We are especially grateful to our dentists who have been pioneers in this field and to our parent representatives who made sure we considered the patient’s perspective. In our discussions we soon realised that we would be unable to review and advise on all aspects of sedation and we decided to limit our searches for evidence that would help guide 90% of scenarios. Nevertheless we wanted to make clear statements of principle that will be applicable and relevant to all situations.

We began by identifying key questions. We wanted to advise on how patients should be assessed, prepared and managed, and to specify the necessary resources. The psychological needs and behavioural management have also been considered. All these were tackled by consensus methods. Other questions related to whether sedation drugs are effective and safe, and we hoped that these could be answered from published evidence. There is a long list of potentially useful drugs but we decided to choose drugs that were in common use in the UK, and those that could be applied to the "90% of scenarios". In particular we chose not to review evidence for analgesia alone except for those that have a sedative component or those that are commonly used in combination with another sedative.

When considering the safety of sedation the concepts of "consciousness", "margin of safety" and "target depth" are important. The ideal safe sedation technique is one that can be relied upon to not cause sedation deeper than the target depth of moderate sedation (also known as conscious sedation). At this level the patient responds to stimuli and vital reflexes are active. Drugs with a wide margin of safety have a large difference between the doses that cause moderate sedation and those that depress vital reflexes.

Propofol and sevoflurane are potent anaesthetic drugs that can be administered in small doses to achieve short acting and controlled moderate sedation. It is debatable whether these drugs can reliably sedate rather than stray unintentionally beyond the target depth into anaesthesia. The truth probably depends upon the dose and the pain of the procedure, and we decided to consider published evidence about these drugs provided the authors had the intention of causing sedation.

Our technical team found surprisingly few high quality published reports and clinical trials. This perhaps was due to the practical difficulties of enrolling sufficient numbers of children into adequately controlled and blinded protocols. We have only considered efficacy data from RCTs but used both cohort studies and RCTs for safety data.

Different procedures need different sedation techniques and we wanted to develop a practical algorithm to facilitate effective and safe decisions. We limited ourselves to four common scenarios and these are: short painful procedures in the emergency department, gastrointestinal endoscopy, dental procedures and painless imaging. We are confident that guidance for these can be applied to 90% of scenarios.

The cost-effectiveness of sedation has to be compared with anaesthesia. The "quality of patient experience" is rarely published in clinical trials and when it did it was difficult to interpret. The cost was the more measurable factor and was the cost of the healthcare practitioners involved. However there was disagreement about whether or not the data described the true "everyday" situation. If sedation fails, its cost must take into account the cost of anaesthesia, and therefore we needed to take account of the failure rate that would make the investment of an anaesthesia service worthwhile.

A change in sedation services to children has become necessary because demand has increased and change is within our grasp if healthcare professionals work together to improve standards. My GDG colleagues and I have been privileged to develop this guideline and it is our sincerest hope that it will make a significant contribution to making diagnostic and therapeutic procedures less distressing and safer for children and young people.

Mike Sury

Chair, Guideline Development Group

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Acknowledgements

The development of this guideline was greatly assisted by the following people:

Emma Nawrocki, Fatema Limbada, Jaymeeni Solanki and Abigail Jones (NCGC Project Coordinators); Tamara Diaz (NCGC Project Manager); Taryn Krause (NCGC Senior Project Manager); Jill Parnham (NCGC Operations Director); Susan Latchem and Sarah Dunsdon (NICE Commissioning Managers); Rachael Paterson and Anne-Louise Clayton (NICE Editors); Laura Bruton and Andrew Gyton (NICE Guidelines Coordinators).

Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring concordance to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives.

Stakeholder Involvement

To be added after consultation

1 Abbreviations

AE	Adverse Event
A&E	Accident and Emergency
AGREE	Appraisal of Guidelines Research and Evaluation
ALS	Advanced Life Support
ANCOVA	Analysis of covariance
ASA	American Society of Anaesthesiologists
BNF	British National Formulary
BLS	Basic Life Support
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CH	Chloral hydrate
CI	Confidence interval
CPR	Cardiopulmonary Resuscitation
CT	Computerised Tomography
CUA	Cost-utility analysis
DH	Department of Health
ED	Emergency Department
F	Fentanyl
GA	General Anaesthesia
GDG	Guideline Development Group
GI	Gastrointestinal
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline Review Panel
HRQL	Health-related quality of life
HTA	Health technology assessment
I	Isoflurane
ICC	Intraclass correlation coefficient
ICER	Incremental cost-effectiveness ratio
ILS	Intermediate Life Support

IM	Intramuscular
IN	Intranasal
INB	Incremental net benefit
Inh	Inhaled
IQR	Inter-quartile range
ITT	Intention to treat
IV	Intravenous
K	Ketamine
LA	Local anaesthesia
LOS	Length of Stay
LY	Life-year
M	Midazolam
MD	Mean Difference
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTC	Mixed-treatment comparisons
NCGC	National Clinical Guidelines Centre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
N2O	Nitrous Oxide
N2O+O2	Nitrous oxide and oxygen
O	Opioids
OGD	Oesophago-Gastro Duodenoscopy
OR	Odds ratio
P	Propofol
PASA	NHS Purchasing and Supply Agency
PICO	Framework incorporating patients, interventions, comparison and outcome
PPIP	Patient and Public Involvement Programme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCA	Royal College of Anaesthetists
RCN	Royal College of Nursing
RCT	Randomised controlled trial
RR	Relative risk
RT	Radiotherapy
S	Sevoflurane
SD	Standard deviation

SR	Systematic review
TS	Triclofos sodium
vs.	Versus

1 Glossary of Terms

Absolute risk reduction (Risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation[106].
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Administration of sedation	Administration of sedation refers to the administration (for example injection) of a sedation drug to a patient
Advanced Life Support	Advanced Life Support is the management of the child or young person who is deteriorating, in respiratory arrest or in cardiac arrest. Senior healthcare professionals (doctors, nurses, paramedics) work together in a structured team environment in managing the child or young person, with advanced skills in airway management and ventilation, chest compression, administration of life support drugs and support to the child or young person's family/carers.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Alternative (dental) sedation techniques	Term used in dentistry to describe sedation techniques other than standard dental sedation techniques (for example, nitrous oxide alone or benzodiazepine) where a drug or drug combinations are used with the intention of producing conscious sedation only. These techniques should carry a margin of safety wide enough for the unintended loss of consciousness to be unlikely.

Anaesthetic agent	A drug used to cause general anaesthesia. Anaesthetic agents are potent and reliably cause anaesthesia but they may be given in low or "sub-anaesthetic" doses to cause sedation. Sedation techniques using anaesthetic agents have been called "narrow margin of safety" techniques because the difference between the sedation dose and the anaesthesia dose is small.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines Research and Evaluation (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after the run-in period where applicable), with which subsequent results are compared.
Basic Life Support	Basic Life Support (in hospital) is the maintenance of a child or young person's airway and support of breathing and the circulation using mask ventilation, simple airway devices or pocket mask. A combination of expired air ventilation (rescue breathing) and chest compression is known as cardiopulmonary resuscitation (CPR).
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as ‘adherence’ or ‘concordance’.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.

Conference proceedings	Compilation of papers presented at a conference.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Conscious sedation	Drug-induced depression of consciousness, similar to moderate sedation, except that verbal contact is always maintained with the patient. This term is used commonly in dentistry. See Moderate sedation-
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Deep sedation	Drug-induced depression of consciousness during which patients are asleep and cannot be easily roused but do respond purposefully to repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
Delivery of sedation	Delivery of sedation refers to an health care professional or team of health care professionals involved in the direct care of a sedated patient (it includes assisting in the administration of sedation and also monitoring and recovery)
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dissociative sedation	A trance-like cataleptic state, with profound analgesia, sedation and amnesia, immobility, preservation of airway reflexes, and (generally) spontaneous respiration and cardiovascular stability.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.

Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.
Drop-out	A participant who withdraws from a clinical trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.

Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
General anaesthesia	Drug-induced loss of consciousness during which patients are not rousable, even by painful stimulation. Patients often require assistance in maintaining a patent airway. Ventilatory function is often impaired. Positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See 'Reference standard'.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Harms	Adverse effects of an intervention.
Healthcare professional	For the purposes of this guideline the term 'healthcare professional' refers to a trained, registered and licensed to practice in the UK and is an individual involved in the care of a sedated patient; this includes doctors, dentists or nurses.
Healthcare professional trained in delivering anaesthetic agents	A healthcare professional with an appropriate skill set who has undertaken specific training in the use of one of more anaesthetic agents to be used for sedation.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.

Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypothesis	A supposition made as a starting point for further investigation.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. $ICER=(Cost_A – Cost_B) / (Effectiveness_A – Effectiveness_B)$.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Index	In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.
Indication (specific)	The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Intermediate Life Support	Intermediate Life Support is the initiation of cardio-pulmonary resuscitation in the clinical setting, including effective chest compressions and ventilation and early safe defibrillation. Those healthcare professionals with intermediate life support skills are able to utilise a wider range of life support adjuncts (such as the laryngeal mask) and should also recognise the child or young person who is at risk of deterioration, therefore preventing cardiac arrest.
Intermediate outcomes	Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study: for example, intraocular pressure reduction is related to the risk of conversion to COAG or COAG progression.
Internal validity	The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	An index which compares the agreement against that which might be expected by chance
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Margin of safety	A term used to describe the difference in the dose of a sedation drug, or combination of drugs, that causes moderate sedation as opposed to deep sedation or anaesthesia.
Markov model	A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Minimal sedation	A drug-induced state during which patients are awake and calm, and respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
Moderate sedation	Drug-induced depression of consciousness during which patients are sleepy but respond purposefully to verbal commands (known as conscious sedation in dentistry), or light tactile stimulation (reflex withdrawal from a painful stimulus is not a purposeful response). No interventions are required to maintain a patent airway. Spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Narrative summary	Summary of findings given as a written description.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Older people	People over the age of 65 years.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.

P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Perioperative	The period from admission through surgery until discharge, encompassing preoperative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	Pertaining to the period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*.
Qualitative research	Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.

Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*.
Secondary benefits	Benefits resulting from a treatment in addition to the primary, intended outcome.
Sedation	Sedation is a state of depressed consciousness. There are depths or levels of sedation that range from minor to major depression of consciousness. Whereas depression of consciousness is a continuum, with no clear boundaries between levels, three levels of sedation have been defined and are in common use: minimal, moderate and deep sedation; they are recommended internationally[1,6,44,196]. The target level of sedation is the level that is intended for the patient. The level of sedation can vary according to the drug, the dose, the patient and the stimulus of the procedure. The level of sedation varies over time due to two main factors: the change in the concentration of the sedation drug within the patient and the variation in the stimulation that opposes sedation.

Sedation, administration of	See ‘administration of sedation’.
Sedation, delivery of	See ‘delivery of sedation’.
Sedation team	A team of health care professionals who are trained to administer sedation drugs and deliver sedation care.
Sedation nurse	A registered nurse trained to both deliver sedation and manage the sedated patient.
Sedationist	A healthcare professional who is trained to both deliver sedation and manage the sedated patient.
Sedative	A drug that causes minimal, moderate or deep sedation. All sedation drugs have a variable effect on conscious level. Some sedation drugs may either not be effective enough or cause sedation deeper than the intended target level. High or excessive doses of drugs may cause unintended deep sedation or anaesthesia. Sedation drugs or techniques that are unlikely to cause anaesthesia have been called drugs with a "wide margin of safety" because they are unlikely to cause appreciable depression of airway reflexes or breathing.
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term ‘Specificity’.

Sensitivity analysis
A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.

Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

Specialist in Sedation
Healthcare professional trained and experienced in delivering sedation using alternative or complex sedation techniques and/or in children and young people with more complex medical conditions.

Specialist sedation techniques
Sedation techniques that have a reduced margin of safety and increased risk of unintended deep sedation or anaesthesia, accompanied by airway obstruction and/or inadequate spontaneous ventilation. Healthcare professionals using specialist sedation techniques need to be trained to administer sedation drugs safely, to monitor the effects of the drug and to use equipment to maintain a patent airway and adequate respiration.

Specialist sedation team
A sedation team trained to administer complex or alternative sedation techniques and/or delivering sedation in children and young people with more complex medical conditions.

Specificity
The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.

See related term 'Sensitivity'.

In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.

Stakeholder
Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

Standard sedation techniques
Sedation techniques that have a wide margin of safety and therefore are unlikely to cause deep sedation.

Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Trained Psychosocial professionals	This is a generic term used to refer to health care professionals, such as play specialists, paediatric nurses, health psychologists, child life specialists (USA only) that are utilised as part of the health care team in a variety of different health care settings. Their training will include knowledge and skills in child development, preparation for sedation, anaesthesia and medical procedures. The list of professionals here is indicative not exhaustive, and training covers key areas relevant to this guideline only.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

1 Introduction

1.1 What is a guideline?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the National Health Service (NHS) – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to the National Institute for Health and Clinical Excellence (NICE) from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establish a guideline development group

- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The National Clinical Guideline Centre and NICE produce a number of versions of this guideline:

- the **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence
- the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies
- the **quick reference guide** presents recommendations in a suitable format for health professionals
- information for the public (‘**understanding NICE guidance’**) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions are available from NICE www.NICE.org.uk.

1.2 The need for this guideline

Many children present to hospitals and dental clinics needing effective sedation or anaesthesia for painful or distressing diagnostic or therapeutic procedures. There are many sedation techniques available but there is insufficient guidance on which techniques are effective and what resources are required to deliver them safely. Sedation is not always effective enough and will occasionally require the procedure to be delayed until the child can be anaesthetised perhaps in another healthcare setting or on another day. Consequently sedation failure is both distressing for the child and has major NHS cost implications. Excessive doses of sedation can cause unintended loss of consciousness and dangerous hypoxia. In comparison, planned anaesthesia is effective, but may have resource implications. The need for sedation or anaesthesia will depend upon the type of procedure. Some types of procedures are very common and healthcare providers and practitioners need to understand whether sedation or anaesthesia is the most cost effective method of managing them

1.3 The National Clinical Guideline Centre

This guideline was commissioned by NICE and developed by the NCGC. The NCGC is one of four national collaborating centres (Cancer, Women and Children’s Health, Mental Health and the NCGC) funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work.

1.4 Remit

The following remit was received by the NCGC from the Department of Health in March 2008 as part of NICE's 18th wave programme of work.

The Department of Health asked NICE:

"To prepare a clinical guideline on sedation for diagnostic and therapeutic procedures in infants, children and young people up to the age of 19."

1.5 What the guideline covers

Clinical need for the guideline:

- In adults, many procedures can be undertaken with local anaesthesia and reassurance. In children and young people this is often not possible because the procedures are too frightening, too painful and need to be carried out in children who may be ill, or in pain or have behavioural problems. Therefore special consideration is necessary for children and young people undergoing procedures that may cause distress.

- It is estimated that more than 2 million children and young people are taken to emergency departments each year following accidental injury. Many of these children and young people will undergo procedures that require sedation. For example, in 2005–6 there were 866 children aged 14 and younger who required a closed reduction of a dislocated joint. Sedation is also frequently used for invasive diagnostic procedures such as lumbar punctures, bone marrow biopsies and endoscopies. In 2005–6 there were 4700 gastroscopies, 9000 diagnostic spinal punctures and 2100 bone marrow biopsies carried out on children aged 14 and younger. Sedation is also commonly used in dental practice where the use of general anaesthesia is now restricted to the hospital setting.

- Sedation is only one of the management options available for children and young people undergoing therapeutic or diagnostic procedures. Non-pharmacological techniques may also be useful in reducing anxiety and managing behaviour, and analgesia may be used to provide pain control. These techniques may be used in combination with sedation or as an alternative to sedation. Another alternative to using sedation for diagnostic or therapeutic procedures is to carry out the procedure under general anaesthesia, in which case the usual standards of care for patients undergoing anaesthesia must be met.

- Sedation is a drug-induced depression of consciousness. The aims of sedation during diagnostic or therapeutic procedures may include reducing fear and anxiety, providing pain control 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) scan; in older children sedation may be necessary to minimise the physical and psychological consequences of a painful procedure such as a lumbar puncture.

- The effect of sedation drugs on consciousness level is a continuum ranging from the awake state, through progressively deeper levels of sedation to anaesthesia. Anaesthesia is an unresponsive state in which vital airway and breathing reflexes are likely to be suppressed. The American Society of Anesthesiologists (ASA) has published useful definitions of sedation levels, classifying them as 'minimal', 'moderate' and 'deep'. Minimal sedation equates to anxiolysis and has no appreciable effect on vital reflexes. In a state of moderate sedation the patient is able to breathe adequately without assistance and responds purposefully to verbal stimulus or tactile stimulation. This is often referred to as conscious sedation. During deep sedation, the patient cannot be roused easily but will respond purposefully to repeated or painful stimuli and may require assistance with their airway or breathing. The level of sedation that is appropriate will depend on the nature of the procedure and the needs of the individual. Deeper levels of sedation require more advanced management because the patient's protective reflexes are affected and they have the potential to progress to anaesthesia.

- The level of sedation achieved depends on the drug used and the dose at which it is given. When choosing between sedation techniques, healthcare professionals must consider the effectiveness of the drug in achieving the required level of sedation, the duration of that effect, and the margin of safety between the dose required to achieve sedation and the dose that is likely to cause anaesthesia.

- There may be serious adverse effects if the level of sedation is greater than intended. If breathing is unintentionally depressed and this complication is not recognised and managed appropriately, then this may lead to hypoxic brain injury or death. Sedation drugs may also have other unexpected adverse effects such as prolonged emergence, paradoxical excitement or post-sedation nausea and vomiting.

- If sedation is unsuccessful, this can result in a painful and traumatic experience for the child. It may be necessary to complete the procedure under general anaesthesia or the procedure may need to be abandoned and rescheduled. If the child becomes distressed due to a failure to provide adequate sedation, their parent or carer may choose to refuse consent for further procedures. A distressing experience may also have long-term psychological consequences for the patient, especially if they are required to undergo repeated procedures.

- There is significant variation in practice across the NHS, with sedation being carried out by a variety of healthcare professionals using a wide range of techniques, within different clinical settings. The Scottish Intercollegiate Guidelines Network (SIGN) published a guideline on this topic in 2004. This covered moderate sedation but not deep sedation, and the evidence base it considered has not been updated since 2002. The aim of this guideline is to provide recommendations to both improve the effectiveness and safety of all types of procedural sedation and to reduce current variations in standards of care.

Groups that will be covered:

- Infants, children and young people (under 19 years) receiving sedation by any technique for painful or non-painful diagnostic or therapeutic procedures.
- The GDG will consider whether different recommendations are required for different age groups in the population.

Healthcare setting:

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

Clinical management

- Assessment of the patient to determine whether sedation is appropriate.
- Clear communication, in a child-friendly manner, of information relating to the preparation required for the procedure or investigation, and related sedation technique. This will include the needs of the patient and their parents or carers, ensuring that implications (sedation safety and efficacy) are clearly understood by both the patient and their parent or carer prior to informed consent.
- Preparation required for the procedure or investigation and related sedation technique.
- The clinical environment, including the availability of equipment, facilities and staff.
- Patient monitoring during and after sedation and criteria for discharge following sedation.
- The effectiveness, safety and limitations of sedation techniques. This will include the use of sedation in combination with non-pharmacological techniques and in combination with analgesia. Note that guideline recommendations will normally fall within licensed indications. Where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics and the 'British National Formulary for Children' to inform their decisions for individual patients.
- The Guideline Development Group (GDG) will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

Training and competence:

- Training for practitioners involved in procedural sedation, irrespective of specialty background, that will be relevant to the sedation techniques and the clinical environment.
- Training that enables practitioners to be competent in the practical aspects of effective and safe delivery of sedation techniques relevant to the clinical situation, and the management of adverse events (for example, airway management skill in the inadvertently anaesthetised patient).

1.6 What the guideline does not cover

Groups that will not be covered

- 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.

1.7 Who developed this guideline?

A multidisciplinary GDG comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

NICE funds the NCGC and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Mike Sury in accordance with guidance from NICE.

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate, however this was not deemed necessary for any group members on this guideline.

2 Methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The guidelines manual' (NICE 2009)[172].

2.1 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the review team and refined and validated by the GDG. The questions were based on the scope (Appendix A).

The full list of clinical questions addressed by the guideline is summarised in the table below.

Full list of clinical questions:

Question	Relevant chapter	Method used to formulate recommendations
Pre-sedation assessment, communication, patient information and consent		
For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques **- what factors should be assessed to justify the use of sedation rather than no sedation or general anaesthesia?**	4	Consensus*
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?**	4	Consensus (as no relevant papers were identified for review)
For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques **- who should make the assessment and how should the assessment be recorded?**	4	Consensus*
For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques **- how should consent be obtained for sedation?**	4	Consensus*
Fasting		
In children and young people under the age of 19 undergoing sedation techniques **- should fasting versus no fasting be implemented to prevent adverse outcomes?**	4	Evidence based (literature review)
Psychological preparation		
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?**	4	Evidence based (literature review)
Personnel and training		
For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation **- what generic and specific skills are required for different team members and for different levels of sedation?**	4	Consensus*
For personnel involved in delivering sedation to children and young people under the age of 19 undergoing diagnostic and therapeutic procedures **- what training and competences are required?**	4	Consensus*
Clinical environment and monitoring		

* Questions denoted with * were agreed with NICE as consensus style questions *a priori*. These questions were based upon stakeholder desire to include these aspects even though routine care. The GDG felt that there would be limited evidence in these areas and as such they were background questions that were not congruent with the style of a full and systematic evidence based approach

Question	Relevant chapter	Method used to formulate recommendations
For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under moderate or deep sedation techniques **- what monitoring and equipment is required to reduce the risk of complications?**	4	Consensus*
When should monitoring stop for children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques?	4	Consensus*
Discharge criteria		
For children and young people under the age of 19 after diagnostic and therapeutic procedures under moderate or deep sedation techniques **- what discharge criteria are required?**	4	Consensus*
Efficacy and safety of midazolam		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Efficacy and safety of ketamine		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Efficacy and safety of chloral hydrate		
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?	6	Evidence based (literature review)

* Questions denoted with * were agreed with NICE as consensus style questions *a priori*. These questions were based upon stakeholder desire to include these aspects even though routine care. The GDG felt that there would be limited evidence in these areas and as such they were background questions that were not congruent with the style of a full and systematic evidence based approach.

Question	Relevant chapter	Method used to formulate recommendations
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?	6	Evidence based (literature review)
Efficacy and safety of nitrous oxide		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Efficacy and safety of opioids		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Efficacy and safety of propofol		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Efficacy and safety of sevoflurane		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)

Question	Relevant chapter	Method used to formulate recommendations
Efficacy and safety of triclofos sodium		
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?	6	Evidence based (literature review)
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?	6	Evidence based (literature review)
Sedation sparing		
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**?	6	Evidence based (literature review)

From these clinical questions, the technical team produced review questions and protocols to address these questions. The protocols are reported in appendix H.

2.2 Searching the literature

2.2.1 Clinical literature search

The search strategies and the databases searched are presented in detail in Appendix C. All searches were conducted on the following databases with no date restrictions.

Database	Interface	Date searched from
Medline	OVID	1950
Embase	OVID	1980
Cinahl	EBSCO	1982
The Cochrane Library (to 2009 Issue 4)	www.thecochranelibrary.com	All dates searched: 1996 for Cochrane Reviews 1995 for DARE 1898 for CENTRAL 1904 for Methods Studies 1995 for HTA and NHSEED

Databases were searched using relevant subject headings and free-text terms. Where appropriate, study design filters were applied. Non-English language studies and abstracts were not reviewed.

All searches were updated to 18th January 2010. Hand-searching was not undertaken following NICE advice that exhaustive searching on every guideline review topic is not practical or efficient[172]. Reference lists of articles were checked for studies of potential relevance.

2.2.2 Sifting process

Once the search had been completed, the following sifting process took place:

- 1st sift: one reviewer sifted the title/abstract for articles that potentially met the eligibility criteria; this was checked where necessary by a second reviewer.
- 2nd sift: full papers were ordered that appeared relevant and eligible or where relevance/eligibility was not clear from the abstract.
- 3rd sift: full papers were appraised that meet eligibility criteria. Generally, one reviewer appraised the papers using an inclusion criteria form, and this was checked where necessary by a second reviewer.

Once individual papers were retrieved, the articles were checked for methodological rigour (see section 2.4), applicability to the UK and clinical significance. Assessment of study quality concentrated on dimensions of internal validity and external validity. At this stage, some studies were excluded if the interventions were not licensed for use in the UK or they were not regularly used in the UK. Studies in which the interventions were obsolete were also excluded.

2.2.3 Economic literature search

Economic evidence was obtained from systematic searches of the following databases in accordance with the NICE Guidelines Manual: Medline, Embase, the Health Technology Appraisals (HTA) database and the NHS Economic Evaluations Database (NHSEED. The latter two databases were searched via The Cochrane Library. Health economics searches were restricted by date on Medline and Embase to studies published since 2006.

Detailed search strategies can be found in Appendix C.

2.3 Clinical effectiveness review methods

This section describes the methods of reviewing that are common to all reviews of intervention studies. Further specific details are given in the individual reviews and in Appendix H. Details on consensus chapters are given in section 2.4.4

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more of the outcomes listed in section 2.3.2. Selected studies were ordered and assessed in full by the NCGC team using agreed inclusion/exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design. Further references suggested by the GDG were assessed in the same way. Not enough data was available from RCTs for serious adverse events related to pharmacological interventions. Consequently, an additional literature review of observational data was performed to supplement the RCT evidence.

2.3.1 Patients covered by this guideline

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.

This guideline will not cover:

- 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.

2.3.2 Outcome measures

The following outcomes were 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), Faces Pain Scale (FPS).
    - 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
    - recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state
    - duration of procedure
    - 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:
    - o external cardiac massage
    - o defibrillation
- Oxygen desaturation <90%
- Vomiting

2.4 Appraising the evidence

2.4.1 Appraisal of methodological quality of 'treatment' studies

Procedure adopted

- For each clinical question, the randomised control trial evidence was sought. If RCT evidence was not available, observational data was also reviewed.
- Randomised control trials (RCTs) were reviewed for drug efficacy and safety outcomes. Only RCTs of N≥20 in each arm were included. The largest available cohort studies were also included for drug safety reviews.
- Studies were appraised for methodological quality using the GRADE[#] scheme. Studies were downgraded or upgraded depending upon their risk of bias using GRADE criteria (see section 2.4.3). As the RCT evidence for this guideline was characterised by small sample sizes, the standard 'default calculations for precision were applied. Rational has been provided when studies were downgraded.
- Meta-analysis of RCT results was performed if the data was sufficiently homogeneous (see section 2.4.2).

2.4.2 Data synthesis for treatment studies

Where possible, meta-analyses were conducted to combine the results of studies for each clinical question using Cochrane Review Manager software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: number of adverse events, and the continuous outcome for endpoint or change from baseline IPSS score, QOL question from IPSS score and Qmax was analysed using an inverse variance method for pooling weighted mean differences. Statistical heterogeneity was assessed by considering the chi-squared test for significance at p<0.1 and an I-squared of ≥ 50% to indicate significant heterogeneity.

[#] GRADE – Grading of Recommendations Assessment, Development and Evaluation

Where significant heterogeneity was present we explored a number of possible predefined differences including the severity or main symptoms experienced by the participants recruited into the study, study design (open label or masked), and length of follow-up by doing subgroup analyses. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

We looked for all outcomes of interest in each paper that was included in the evidence reviews. Where a primary or important decision-making outcome was not reported by a paper, these were not included in the evidence statements or GRADE profiles, in order to highlight an 'absence of evidence'. Where studies reported there were 'no events' for an outcome, this has been denoted in the review evidence statements or GRADE profiles as '0' patients, '0%' or 'no events'.

2.4.3 Grading evidence

The GRADE scheme (GRADE working group 2004) was used to assess the quality of the evidence for each outcome not each study, using the approach described below.

The following features were assessed for the evidence found for each relevant outcome from a systematic review:

- study design (as a proxy for bias)
- limitations in the methodological quality of the study (mainly allocation concealment, blinding and loss to follow-up)
- consistency of an effect across studies
- directness (the degree to which the results directly address the question posed or, for example, are for a somewhat different population).

Other considerations:

- imprecision[♣]
- likelihood of reporting bias

[♣] Precision requires the GDG to decide what are clinically important harms and benefits for that outcome measure. For dichotomous outcomes we used a relative risk reduction of 25% (RR of 1.25 or 0.75) to indicate the clinically important threshold. For positive outcomes, the upper clinically important threshold used depended on the control group rate. When this rate was less than 80% a value of 1.25 was used. When the control group rate was more than 80%, the clinically important threshold was calculated assuming an intervention group rate of 100% and a control group rate based on the median rate where there was more than one study.

- strength of association
- evidence of a dose–response relationship
- expected effect of plausible confounders.

Evidence summaries (evidence profiles) were produced for each outcome

The procedure adopted when using GRADE was:

- A quality rating was assigned, based on the study design.
- This rating was up- or down-graded according to specified criteria: study quality, consistency, directness, preciseness and reporting bias. Criteria were given a downgrade mark of −1 or –2 depending on the severity of the limitations.
- The downgrade/upgrade marks were then summed and the quality rating revised. For example, a decrease of –2 points for an RCT would result in a rating of 'low'. Reasoning was explained for the downgrade marks.

According to GRADE quality assessments, the evidence is classified as follows:

- High: further research is very unlikely to change our confidence in the estimate of effect
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low: any estimate of effect is very uncertain.

The GRADE scheme was only used to assess the quality of evidence for RCTs. Full evidence profiles for efficacy and safety were produced and are contained on the relevant drug section.

The GDG recognised that research from non RCT observational studies is subject to the usual limitations of observational work, including dependence on the quality of medical record documentation and potential for bias secondary to non randomisation, and un-blinded participants. In these studies, there were no interventions or comparisons but merely data collection of adverse events. The datasets were generally large, and were expected to provide more information on a range of adverse events than the small RCTs available for review. Due to these limitations, we only assigned quality rating ('very low' quality) based on the GRADE scheme. It was considered more comprehensive to present separately this supplementary observational data in the form of concise, customised summary tables which also contain the GRADE ratings.

2.5 Consensus

There are generally three main methods reported for developing consensus. These are Delphi, consensus development panels and nominal group processes[33]. The nominal group technique (NGT) was originally developed by Delbecq et al[52] as an organisational planning tool. The methodology varies from the Delphi process, which by design allows individuals to work in the presence of others, but verbal interaction is discouraged and facilitated through sequential questionnaires or summary processes, enabling consensus to be developed without the social pressures normally exerted through open dialogue[238]. Individual ideas are shared within the group, with facilitated discussion enabling the group to see how individuals are expressing their ideas. Normal practice is for the facilitator to then ask the group to prioritise, with aggregated rankings recorded. NGT uses this approach but with participant dialogue encouraged. This methodology works extremely well in clinical guideline development for those clinical questions identified and agreed as areas to be explored through consensus process, and towards the end of guideline development and in particular when working with the GDG in prioritising recommendations for targeted implementation.

The GDG in working together for a fourteen month period during development of the guideline is by nature a mature working group; individuals within the group are able to express their views relating to key issues in relation to clinical questions and key recommendations addressed through consensus methods within a social setting (the last GDG meeting). This is important for the group, who are able to use this experience and the content of discussion to then go into a formal agreement of consensus recommendations and formal voting as part of recommendation sign off. Developing consensus through validated instruments is important in ensuring the integrity of final recommendations that reflect the group as a whole, and benefit from the wealth of clinical and patient experience considered. The process itself enables all constituent members of the GDG to have equal weighting of opinion as their opinion moves towards a consensus group position. Typically, NGT works well for small groups, with 12 to 15 people widely acknowledged in the literature as the maximum number of people involved in this process.

2.6 Cost-effectiveness review methods

Economic evaluations are useful in guideline development as they assess the costs and benefits of alternative courses of action which could be recommended within the guideline. Relevant published economic information may be used by the GDG to determine whether a particular recommendation would result in the efficient use of NHS resources, but in order to do so it must provide an estimate of both the costs to the NHS and the health benefits to patients. Relevant study designs are cost-effectiveness, cost-utility or cost-benefit analyses. Cost-minimisation analyses are only relevant when supported by evidence demonstrating that there is no difference in health outcome between the alternative health care interventions. Cost studies which focus solely on the cost of alternative health care interventions are not suitable for informing decisions on the efficient use of NHS resources as they do not take into account any differences in the benefits for patients. Studies reporting analyses in non-OECD member countries or prior to 1990 were also excluded as these were felt to be less relevant to current practice in the UK.

We have excluded analyses where the estimates of clinical effectiveness used to inform the economic evaluation are not based on evidence from randomised controlled trials (RCTs) or quasi-randomised controlled trials. This was done to minimise the potential for bias and to ensure consistency with the clinical effectiveness reviews.

The search strategy for existing literature is described in section 2.2.3 (Economic literature search). There were 226 papers identified by the search. After considering titles and abstracts, 24 papers were identified as potential cost or cost-effectiveness studies and all of these were ordered to cross check whether they reported both cost and health outcomes even in a disaggregated way.

Of the 24 full text papers considered, 7 were found to be not relevant to the review question as they were found either to report clinical outcomes only, or they compared interventions that were not relevant to the guideline, or they were in predominantly adult populations (minimum age of 16 and a mean age >45).

Of the 17 remaining studies, 12 were economic evaluations carried out within studies using non-RCT designs in which the estimates of clinical effectiveness were considered to be open to bias due to the trial design. These were excluded from the cost-effectiveness review. A list of the excluded studies and reasons for exclusion are listed in appendix F. Two (Martinez 2002[160], Iannalfi 2005[99]) of the remaining 5 studies were economic evaluations carried out within RCTs and three (Lee 2000[137], Jameson 2007[101], Pershad 2006[181]) were model based evaluations. A description of the five studies is also given in appendix F. We carried out update searches up to 18th January 2010 but did not identify further useful studies.

None of the identified five studies was of high quality, and they provided little relevant evidence on the cost-effectiveness of sedation techniques considered in the guideline. It was therefore necessary to construct an original economic evaluation model to determine the cost-effectiveness of sedation techniques.

2.7 Cost-effectiveness modelling

The details of the economic model are described in Appendix F.

Cost-effectiveness information helps the GDG to weigh the balance of the cost and health benefit of applying intervention strategies in the different population groups considered in the guideline. At the early stages of the sedation guideline development, the health economist worked with the GDG to identify two high priority areas for cost-effectiveness evidence. The first area of priority was on the cost-effectiveness evidence to enable the GDG determine which sedation technique is most appropriate. The second area was on the cost-effectiveness of using a combination of non-pharmacological techniques and sedation drugs as sedation sparing technique.

These were classified as high priority because appropriate sedation technique should have the potential to prevent the need to abandon and reschedule procedures when sedation is unsuccessful. This will reduce the use of the National Health Services (NHS) or Personal Social Services (PSS) resources. It should minimise distress, discomfort for and risk of harm to patients as well as reduce the potential for QALY loss due to long term morbidity or mortality. There was the need to gather health economic information on different sedation strategies. As we did not identify directly applicable reports, it became necessary to consider carrying out a *de novo* economic evaluation to determine the cost-effectiveness of different techniques.

We did not construct any cost-effectiveness model for using a combination of non-pharmacological techniques and sedation drugs as sedation sparing technique. The GDG did not consider it worthwhile to build this model as there was no evidence that a combination of non-pharmacological techniques and sedation drugs has a sedation sparing effect (see 6.11). The health economic work for this guideline was therefore focused on the first area of priority, the most appropriate sedation technique.

Cost-effectiveness was determined by comparing the cost per patient for the different strategies. The technique with the lowest cost per patient is considered to be the optimal strategy from a cost-effectiveness perspective on the basis that:

- for those interventions included in the model, there was no evidence that one technique was safer than another; and
- we costed the whole pathway to completion of procedure.

The model was constructed using the best available evidence. Clinical and safety evidence was taken from a systematic review (chapter 6 on clinical effectiveness and safety review) and costing was based on the perspective of the NHS and personal social services. 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.

We did not do a probabilistic sensitivity analysis as the estimates for a number of key input parameters were ascertained by expert opinion. However, we did conduct one-way and threshold sensitivity analyses to explore parameter uncertainty. The limitations of the model are discussed.

We have not prioritised all the clinical questions for economic evaluation. For those which were not prioritised, the GDG considered the likely cost-effectiveness of available options by making a qualitative judgement on the likely costs, health benefits and potential harms. In particular, mild and moderate sedation was found to be considerably less costly than deep sedation and general anaesthesia in appropriately selected patients and this finding is reflected in the recommendations throughout the guideline.

2.8 Developing recommendations

Over the course of the guideline development process, the GDG was presented with the following:

- The clinical and economic evidence reviews. All evidence tables are in Appendices D, E and G.
- Forest plots of results from studies, including meta-analyses where appropriate.
- A description of the methods and results of the cost-effectiveness analysis

Recommendations were drafted on the basis of this evidence whenever it was available.

When clinical and economic evidence was poor or absent, the GDG proposed recommendations based on their expert opinion.

The GDG also developed a care pathway algorithm according to the recommendations.

2.9 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

The GDG identified four high priority research recommendations, after discussion and voting (appendix G).

2.10 Validation of the guideline

The first draft of this guideline was posted on the NICE website for an 8-week consultation period between 17 May and 12 July 2010, and registered stakeholders were invited to comment. The GDG responded to comments and an amended version of the guideline was produced.

2.11 Disclaimer and funding

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaim any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

The Collaborating Centre for Nursing and Supportive Care (now a part of the National Clinical Guideline Centre) were commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

2.12 Updating the guideline

This guideline will be updated in concordance with NICE guidelines manual (NICE 2009)[172].

3 Summary of Recommendations

Below are the recommendations that the GDG selected as the key priorities for implementation followed by the complete list of recommendations and research recommendations.

3.1 Key priorities for implementations

The GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients (**A**)
- Have a high impact on reducing variation in care and outcomes (**B**)
- Lead to a more efficient use of NHS resources (**C**)
- Promote patient choice (**D**)
- Promote equalities.(**E**)

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Relates to an intervention that is not part of routine care (**U**)
- Requires changes in service delivery (**V**)
- Requires retraining staff or the development of new skills and competencies (**W**)
- Highlights the need for practice to change (**X**)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (**Y**)
- May be viewed as potentially contentious, or difficult to implement for other reasons (**Z**)

For each key recommendation listed below, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.

- ❖ Ensure that trained healthcare professionals (see section on personnel and training) carry out pre-sedation assessments and document the results in the healthcare record.

(Selection criteria: A, B, C, D, E. Implementation support: W, X, Y)

- ❖ Establish suitability for sedation by assessing all of the following:
  - current medical condition and any surgical problems
  - weight (growth assessment)
  - past medical problems (including any associated with previous sedation or anaesthesia)
  - current and previous medication (including any allergies)
  - physical status (including the airway)
  - psychological and developmental status.

(Selection criteria: A, B, C, D, E. Implementation support: W, X, Y)

- ❖ Seek advice from a specialist before delivering sedation:
  - if there is concern about a potential airway or breathing problem
  - if the child or young person is assessed as American Society of Anesthesiologists (ASA) grade 3 or greater
  - for infants, including neonates.

(Selection criteria: A. Implementation support: W)

- ❖ Ensure that both the following will be available during sedation:
  - a healthcare professional and assistant trained (see section on personnel and training) in delivering and monitoring sedation in children and young people
  - immediate access to resuscitation and monitoring equipment (see section on clinical environment and monitoring).

(Selection criteria: A, B. Implementation support: V, W, X, Y)

- Choose the most suitable sedation technique based on all the following factors:
    - what the procedure involves
    - target level of sedation
    - contraindications
    - side effects
    - patient (or parent or carer) preference.

(Selection criteria: A, B, C, D, E. Implementation support: W, X, Y)

- Healthcare professionals delivering sedation should have knowledge and understanding of and competency in:
    - sedation drug pharmacology and applied physiology
    - assessment of children and young people
    - monitoring
    - recovery care
    - complications and their immediate management, including paediatric life support.

(Selection criteria: A, B. Implementation support: U, W, X, Y, Z)

- Healthcare professionals delivering sedation should have practical experience of:
    - effectively delivering the chosen sedation technique and managing complications
    - observing clinical signs (for example, airway patency, breathing rate and depth, pulse, pallor and cyanosis, and depth of sedation)
    - using monitoring equipment.

(Selection criteria: A, B. Implementation support: U, W, X, Y)

- Ensure that members of the sedation team have the following life support skills:

	Minimal sedation*	Moderate sedation	Deep sedation
All members	Basic	Basic	Basic
At least one member		Intermediate	Advanced

* including sedation with nitrous oxide alone (in oxygen) and conscious sedation in dentistry.

(Selection criteria: A, B. Implementation support: U, W, X, Y, Z)

- Healthcare professionals delivering sedation should have documented up-to-date evidence of competency including:
  - satisfactory completion of a theoretical training course covering the principles of sedation practice
  - a comprehensive record of practical experience of sedation techniques, including details of:
    - sedation in children and young people performed under supervision
    - successful completion of work-based assessments.

(Selection criteria: A, B. Implementation support: U, W, X, Y, Z)

- For deep sedation continuously monitor, interpret and respond# to all of the following:
  - depth of sedation
  - respiration
  - oxygen saturation
  - heart rate
  - three-lead electrocardiogram
  - end tidal CO2 (capnography)*
  - blood pressure (monitor every 5 minutes)*
  - pain
  - coping
  - distress.

#For deep sedation, the healthcare professional administering sedation should be involved only in continuously monitoring, interpreting and responding to all of the above.

* End tidal CO_2 and blood pressure should be monitored, if possible, provided that monitoring does not cause the patient to awaken and so prevent completion of the procedure.

(Selection criteria: A, B. Implementation support: U, W, X, Y, Z)

3.2 Complete list of recommendations

3.2.1 Recommendations on pre-sedation assessment, communication, patient information and consent

1. Ensure that trained healthcare professionals (see section on personnel and training) carry out pre-sedation assessments and document the results in the healthcare record.

2. Establish suitability for sedation by assessing all of the following:
   - current medical condition and any surgical problems
   - weight (growth assessment)
   - past medical problems (including any associated with previous sedation or anaesthesia)
   - current and previous medication (including any allergies)
   - physical status (including the airway)
   - psychological and developmental status.

3. Seek advice from a specialist before delivering sedation:
   - if there is concern about a potential airway or breathing problem
   - if the child or young person is assessed as American Society of Anesthesiologists (ASA) grade 3 or greater
   - for infants, including neonates.

4. Ensure that both the following will be available during sedation:
   - a healthcare professional and assistant trained (see section on training) in delivering and monitoring sedation in children and young people

- immediate access to resuscitation and monitoring equipment (see section on monitoring).

5. Choose the most suitable sedation technique based on all the following factors:
   - what the procedure involves
   - target level of sedation
   - contraindications
   - side effects
   - patient (or patient or carer) preference.

6. To enable the child or young person and their parents or carers to make an informed decision, offer them verbal and written information on all of the following:
   - proposed sedation technique
   - the alternatives to sedation
   - associated risks and benefits.

7. Obtain and document informed consent for sedation.

3.2.2 Recommendations on fasting

8. Before starting sedation, confirm and record the time of last food and fluid intake in the healthcare record.

9. Fasting is not needed for:
   - minimal sedation
   - sedation with nitrous oxide and oxygen
   - moderate sedation during which the child will maintain verbal contact with the healthcare professional.

10. Apply the 2-4-6 fasting rule[a] for elective procedures using any sedation technique other than those in recommendation 9 (that is, for deep sedation and moderate sedation during which the child might not maintain verbal contact with the healthcare professional).

11. For an emergency procedure in a child or young person who has not fasted, base the decision to proceed with sedation on the urgency of the procedure and the target depth of sedation.

3.2.3 Recommendations on psychological preparation

12. Ensure that the child or young person is prepared psychologically for sedation by offering information about:
    - the procedure
    - what the child or young person should do and what the healthcare professional will do
    - the sensations associated with the procedure (for example, a sharp scratch or numbness)
    - how to cope with the procedure.

13. Ensure that the information is appropriate for the developmental stage of the child or young person and check that the child or young person has understood the information.

14. Offer parents and carers the opportunity to be present during sedation if appropriate. If a parent or carer decides to be present, offer them advice about their role during the procedure.

[a] Fasting times should be as for general anaesthesia:
- 2 hours for clear fluids
- 4 hours for breast milk
- 6 hours for solids.

15. For an elective procedure, consider referring to a mental health specialist children or young people who are severely anxious or who have a learning disability.

3.2.4 Recommendations on personnel and training

16. Healthcare professionals delivering sedation should have knowledge and understanding of and competency in:
    - sedation drug pharmacology and applied physiology
    - assessment of children and young people
    - monitoring
    - recovery care
    - complications and their immediate management, including paediatric life support.

17. Healthcare professionals delivering sedation should have practical experience of:
    - effectively delivering the chosen sedation technique and managing complications
    - observing clinical signs (for example, airway patency, breathing rate and depth, pulse, pallor and cyanosis, and depth of sedation)
    - using monitoring equipment

18. Ensure that members of the sedation team have the following life support skills:

	Minimal sedation*	**Moderate sedation**	**Deep sedation**
All members	Basic	Basic	Basic
At least one member		Intermediate	Advanced

*including sedation with nitrous oxide alone (in oxygen) and conscious sedation in dentistry.

19. Ensure that a healthcare professional trained in delivering anaesthetic agents (see appendix J) is available to administer:
    - sevoflurane[b]
    - propofol[c, d]
    - opioids[m] combined with ketamine[m, e].

20. Healthcare professionals delivering sedation should have documented up-to-date evidence of competency including:
    - satisfactory completion of a theoretical training course covering the principles of sedation practice
    - a comprehensive record of practical experience of sedation techniques, including details of:
        - sedation in children and young people performed under supervision
        - successful completion of work-based assessments.

21. Each healthcare professional and their team delivering sedation should ensure they update their knowledge and skills through programmes designed for continuing professional development.

22. Consider referring to an anaesthesia specialist a child or young person who is not able to tolerate the procedure under sedation.

3.2.5 Recommendations on clinical environment and monitoring

23. For moderate sedation excluding with nitrous oxide alone (in oxygen) continuously monitor, interpret and respond to changes in all of the following:

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[b] Sevoflurane is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) sevoflurane did not have UK marketing authorisation for this indication. See appendix J.
[c] Propofol is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) propofol did not have UK marketing authorisation for this age group. See appendix J.
[d] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.
[e] Ketamine is a dissociative agent: the state of dissociative sedation cannot be readily categorised as either moderate or deep sedation; the drug is considered to have a wide margin of safety.

- depth of sedation
- respiration
- oxygen saturation
- heart rate
- pain
- coping
- distress.

24. For deep sedation continuously monitor, interpret and respond# to changes in all of the following:
    - depth of sedation
    - respiration
    - oxygen saturation
    - heart rate
    - three-lead electrocardiogram
    - end tidal CO_2 (capnography)*
    - blood pressure (monitor every 5 minutes)*
    - pain
    - coping
    - distress.

#For deep sedation, the healthcare professional administering sedation should be involved only in continuously monitoring, interpreting and responding to all of the above.

*End tidal CO_2 and blood pressure should be monitored, if possible, provided that monitoring does not cause the patient to awaken and so prevent completion of the procedure.

25. Ensure that data from continuous monitoring during sedation are clearly documented in the healthcare record.

26. After the procedure, continue monitoring until the child or young person:

- has a patent airway
- shows protective airway and breathing reflexes
- is haemodynamically stable
- is easily roused.

3.2.6 Recommendation on discharge criteria

27. Ensure that all of the following criteria are met before the child or young person is discharged:
    - vital signs (usually body temperature, heart rate, blood pressure and respiratory rate) have returned to normal levels
    - the child or young person is awake (or returned to baseline level of consciousness) and there is no risk of further reduced level of consciousness
    - nausea, vomiting and pain have been adequately managed.

3.2.7 Recommendations on painless imaging

28. Do not routinely use ketamine[m, n] or opioids[m] for painless imaging procedures.

29. For children and young people who are unable to tolerate a painless procedure (for example during diagnostic imaging) consider one of the following drugs, which have a wide margin of safety:
    - chloral hydrate[f] for children under 15kg
    - midazolam[g]

[f] Chloral hydrate is used in UK clinical practice for sedating children and young people for painless procedures. At the time of publication (December 2010) chloral hydrate did not have UK marketing authorisation for this indication. See appendix J

[g] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.

30. For children and young people who are unable to tolerate painless imaging with the above drugs, consider one of the following, used in specialist techniques, which have a narrow margin of safety (see section on training):

    - propofol[l, m]
    - sevoflurane[k].

3.2.8 Recommendation on painful procedures

31. In children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation), when the target level of sedation is minimal or moderate, consider:

    - nitrous oxide (in oxygen) and/or
    - midazolam[t] (oral or intranasal)

32. For all children and young people undergoing a painful procedure, consider using a local anaesthetic, as well as a sedative

33. For children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation) in whom nitrous oxide (in oxygen) and/or midazolam (oral or intranasal) are unsuitable consider :

    - ketamine[m, n] (intravenous or intramuscular)
    - intravenous midazolam[t] with or without fentanyl[m] (to achieve moderate sedation)

34. For children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation) in whom ketamine (intravenous or intramuscular) or intravenous midazolam with or without fentanyl (to achieve moderate sedation) are unsuitable, consider a specialist sedation technique such as propofol[l] with or without fentanyl[m].

3.2.9 Recommendation on dental procedures

35. For a child or young person who cannot tolerate a dental procedure with local anaesthesia alone, to achieve conscious sedation consider:

    - nitrous oxide and oxygen or
    - midazolam[t].

    If these sedation techniques are not suitable or sufficient, refer to a specialist team for an alternative sedation technique.

3.2.10 Recommendations on endoscopy

36. Consider intravenous midazolam[†] to achieve minimal or moderate sedation for upper gastrointestinal endoscopy.

37. Consider fentanyl[m] (or equivalent opioid) in combination with intravenous midazolam[†] to achieve moderate sedation for lower gastrointestinal endoscopy.

3.3 Algorithms

See separate file [Algorithm 1]

See separate file [Algorithm 2]

3.4 Research recommendations

3.4.1 Research recommendation on pre-sedation assessment, communication, patient information and consent

- For children and young people under the age of 19 having diagnostic and therapeutic procedures under sedation, what factors should be assessed to establish the need for sedation and reduce the risk of adverse events?

Why it is important

Some children need sedation, some need anaesthesia, and some need behavioural management alone. There is wide variation in how this choice is made. A recommended standard method of assessment could reduce variation and improve both success and safety when sedation is chosen. Furthermore, an assessment tool could help prevent unsuitable choices and improve the overall management of procedures in children. The GDG suggests an observational study to determine the important factors, followed by a consensus study to develop a tool. The assessment tool should be tested by a randomised comparison of children and young people who have been assessed routinely with those who have been assessed using the tool. The aim is for the assessment tool to improve sedation success and quality, and reduce any complications.

3.4.2 Research recommendation on fasting

- For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation how long should they be fasted to prevent adverse events?

Why it is important

Inhalation of gastric contents can be fatal. Loss of consciousness is associated with the loss of vital airway reflexes and inhalation of gastric contents is possible. Consequently, fasting (in order to keep the stomach empty) is standard practice before general anaesthesia and has become standard before any sedation technique that may cause loss of consciousness. Prolonged fasting, however, is distressing and can cause dehydration and hypoglycaemia. It would be helpful to know the minimum length of time necessary to fast a child before sedation in order to ensure that the stomach is empty, and to know that likelihood of regurgitation or vomiting is very small.

3.4.3 Research recommendation on psychological preparation

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures under sedation what psychological techniques can lead to sedation sparing, improve patient/family satisfaction and ensure safe completion of the procedure?

Why it is important

Psychological interventions in children and young people are used extensively in combination with pharmacological interventions for the management of painful medical procedures and for pre- and post-operative distress and pain management after anaesthesia. Similar data are lacking for children undergoing diagnostic and therapeutic procedures under sedation. However, a significant body of literature shows sedation sparing, reduced incidence of side effects and increased satisfaction in adults undergoing various procedures under sedation when combined with psychological interventions such as hypnosis. Randomised controlled trials testing the efficacy of the combination of psychological interventions with sedation versus sedation on its own will allow us to determine whether adding psychological interventions to patient management under sedation is beneficial for children and young people.

3.4.4 Research recommendation on personnel and training

- For personnel involved in delivering sedation to children and young people under the age of 19 having diagnostic and therapeutic procedures what training is required to achieve and maintain essential skills?

Why it is important

Potent drugs can cause unintended airway obstruction. Anaesthetists are skilled at managing airway obstruction because they practise the skills regularly. However, anaesthetists are a scarce resource so non-anaesthetists need to learn how to manage airway obstruction. The skills that are needed have been identified but can these skills be attained and maintained by professionals who need them only occasionally? The GDG suggests that a standard teaching method and assessment tool are developed. This would involve an observational study of a cohort of trainees, who can be assessed, trained and then reassessed at intervals to determine whether the training is successful and how often it is necessary.

3.4.5 Research recommendation on clinical environment and monitoring

- Which depth of anaesthesia monitors can be used to monitor depth of sedation in children and which is best?

Why it is important

Several depth of anaesthesia monitors are in use around the world. Most use processed EEG signals while some use stimulation of the brainstem by auditory stimuli. It is not yet clear whether the available monitors can follow children through different levels of sedation accurately and this study would set out to determine which monitor best tracks the transition from moderate to deep sedation in children of different ages.

3.4.6 Research recommendations on drugs for sedation in infants, children and young people

- For children and young people under the age of 19 having minor painful procedures, what potent analgesic drugs can be combined with midazolam to provide safe moderate sedation?

Why it is important

Midazolam has a strong safety profile in inducing either minimal or moderate sedation. For painful procedures midazolam should be combined with analgesia. Ideally, analgesia is achieved by local anaesthesia. Sometimes local analgesia is insufficient and potent opioid analgesia is necessary. The combination of potent opioid and midazolam can cause deep sedation and airway obstruction. These effects can be managed safely but involve extra resources. It would be safer if a technique could be developed that was both reliable and had a wide margin of safety. Prospective and retrospective audit data are available to help guide the choice of opioid and the doses. A randomised controlled trial is needed to test the efficacy and safety of these combinations.

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures under sedation with ketamine, how can the vomiting be reduced?

Why it is important

Ketamine is demonstrated to have a strong efficacy and safety profile in enabling safe sedation and as an analgesic drug useful for painful procedures in children and young people. Its main side effect is vomiting in approximately 10% of patients. No data is available on whether antiemetic drugs prevent vomiting. The GDG suggested an RCT study comparing ketamine + placebo versus ketamine with antiemetic

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, are procedures carried out under sedation more safe, effective and cost effective than those carried out under general anaesthesia?

Why it is important

Anaesthesia or an “Anaesthetist led service” has the advantage over sedation because it usually has faster onset and offset and is more predictable. It generally requires admission to hospital; it may be more expensive and is a scarce resource. Data comparing the efficiency of sedation in comparison with anaesthesia for certain procedures are not available. Models of care need to be developed and studied to whether anaesthesia or sedation gives the best value for money. With such data, efficient services can be planned.

- For children and young people under the age of 19 undergoing endoscopy, is propofol (with or without: analgesia, another drug or psychological techniques) effective, safe and cost effective for sedation (at minimal and moderate levels) in comparison with midazolam (with or without opioids) or with general anaesthesia?

Why it is important

Propofol is a short acting anaesthetic agent that can be used to achieve any target sedation level. The dose necessary for gastrointestinal endoscopy however usually has a tendency to cause anaesthesia albeit for a short period of time. It would be helpful to know the dose limitation that is unlikely to cause deep sedation because this dose may be effective and well tolerated enough. Moderate sedation with propofol could be compared with another sedation technique such as midazolam with or without opioid. It could also be compared with a general anaesthetic dose of propofol.

- For children and young people under the age of 19 undergoing painful procedures, is propofol effective and safe for sedation in comparison with ketamine?

Why it is important

Both ketamine and propofol are well tolerated and effective drugs suitable for painful procedures. Propofol however has a tendency to cause deep sedation and anaesthesia in which the airway and breathing may need an intervention or support. Ketamine has few appreciable effects on the airway and breathing but has a longer recovery time than propofol and causes vomiting.

- What are the safety and efficacy profiles of sedation techniques in current practice?

Why it is important

There are no data on the safety of sedation in the UK. A large prospective database of sedation cases, that includes data on drugs, procedures, the depth of sedation and complications, would help to define the safety of sedation and actively promote safe practice. The GDG suggests that a national registry for paediatric sedation is established to help create a database with sufficient data.

- Is patient-controlled sedation with propofol feasible in adolescents and children?

Why it is important

Propofol in low dose is an excellent anxiolytic. Patient-controlled sedation has been validated in adults undergoing dental procedures and endoscopy for safety and efficacy. Giving the patient control of their sedation has important psychological benefits. The study would involve developing new pump technology, paediatric software and a child friendly patient-activation system. There would have to be an open pilot evaluation to establish safety and efficacy followed by a randomised-controlled trial versus IV midazolam.

4 Key considerations in supporting the patient's journey

The patient journey is the experience of the patient and their family or carers before, during and after sedation for a procedure. It includes key stages of management by healthcare professionals including patient assessment and preparation. Each stage of the journey has been considered by the GDG for the purpose of maximising the success and safety of sedation. It is the healthcare practitioners themselves who will ensure that sedation is managed well and therefore their training has been discussed at length.

4.1 Pre-sedation assessment, communication, patient information and consent

4.1.1 Clinical introduction

Assessment of the patient is crucial to determine their needs for the procedure. Some patients will cooperate or tolerate procedures without alteration of their conscious level. Other patients will need sedation and the target level will vary according to the patient and the procedure. For example, the target sedation level for dental procedures is conscious sedation whereas a small child having an MRI scan needs to be unconscious either by deep sedation or anaesthesia. Many patients will have medical problems that could give rise to difficulties with sedation and anaesthesia. These will need careful assessment so that the risks of any chosen sedation technique can be appreciated. Communication of all these factors to the patient and their family is important to the consenting process. The presentation of clear and relevant information is likely to help patients and their families make reasoned choices.

4.1.2 Clinical methodological introduction

CLINICAL QUESTIONS:

For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques:

1. What factors should be assessed to justify the use of sedation rather than no sedation or general anaesthesia?
2. What validated tools should be used to support assessment?
3. Who should make the assessment and how should the assessment be recorded?
4. How should consent be obtained for sedation?

Clinical questions 1, 3 and 4

The GDG sought to provide guidance to these questions based on their expert experience and opinion.

Clinical question 2

The literature was searched but no relevant papers were identified for review.

4.1.3 GDG discussion on pre-sedation assessment, communication, patient information and consent

Factors to consider in assessment

The GDG agreed that clear guidance should be given about the components of the assessment of a child or young person prior to sedation. These components feature in the recommendation and, although others may be important, the specified components were considered to be essential and have been arranged in order of priority.

The assessment should begin by understanding the child or young person's medical (or surgical) problem that has led them to require the procedure. Other non-related problems or illnesses, such as diabetes mellitus or an upper airway viral infection, should be identified and assessed. Measurement of the body weight is a simple method of identifying children who are not following normal growth development (or those who are obese). Growth failure may suggest that the disease is severe. Obesity is associated with other medical problems and can impair effective breathing during deep sedation. The doses of all drugs, except vapours and gases, should be calculated or adjusted according to the body weight. In obese children drug doses should be calculated according to an estimated ideal body weight.

Details of previous sedation or anaesthesia, or any medication, may identify problems that can be avoided. An assessment of the airway, breathing and circulation may find dangerous risk factors and problems that require additional equipment and technical expertise. Pulse oximetry is a reliable estimate of oxygen saturation of arterial blood and heart rate. The GDG considered that this tool should be available in the pre-sedation assessment because it is easy to use and will identify some important respiratory and cardiovascular problems.

Some problems are well known to increase the risk of sedation so the benefit of the intended procedure needs to be considered. Physical examination requires training and experience.

Access to the patient's healthcare record is essential for information about previous problems with sedation or anaesthesia.

Children and young people who are unable to understand or cooperate with the sedation may be identified by assessment of their psychological and developmental status. Pre-sedation assessment should establish what the patient is able to understand and appreciate. This aids communication and gains assent. It should be determined if restraint or clinical holding have been used previously and how this was managed. Guidance on the appropriate use of restraint in children has been published by the Royal College of Nursing[7].

The GDG discussed assessment of sedation in the emergency situation. It was agreed that in an emergency the medical needs should take priority until the patient has been stabilized. Once the child or young person has been stabilized, they can be assessed for sedation.

The GDG considered that it was important to make sure that there were safe facilities available to deliver the chosen sedation technique, and this led to discussion about who should be present and what equipment was necessary. The number of required healthcare professionals and the type of equipment were discussed. The GDG emphasized that these resources are essential and need to be present during sedation. Having them nearby may not prevent a problem soon enough, so they need to be next to the patient. If there is a respiratory complication, the healthcare professional will need to react promptly. If monitoring is used effectively, most problems will be prevented and others will be identified as soon as possible. Resuscitation equipment needs to be ready at hand. This includes airway and breathing devices that may need to be inserted promptly to avoid or treat hypoxia and cardiac arrest.

The GDG discussed how many healthcare professionals were needed according to the type of sedation and the intended procedure. It was noted that for some procedures the professional performing the procedure could control or assist in the sedation. In other situations two professionals were needed to concentrate on the patient during sedation and could not therefore be involved in the procedure. Overall, two professionals have to be available to look after a sedated patient; one of these may be involved with procedure provided they can stop the procedure and help with any complications of sedation.

Use of validated tools in assessment

As no evidence was found to support the use of validated tools in the assessment of children prior to sedation, the recommendations are based on the specialist experience and opinion of the GDG.

There are no validated tools for assessment of children and young people for sedation. There is, however, a widely used American Society of Anesthiologists (ASA)[1,6,44] scoring tool to grade risk in patients having anaesthesia. The GDG considered that this was widely understood, simple to use and therefore should be used in describing the physical status of children and young people who need sedation. The sedation management of a patient who is assessed at ASA grade 3 or 4 should be managed after discussion with a specialist in sedation or anaesthesia.

Who should make the assessment?

Whichever professional group is involved with sedation, assessment of children and young people should be sufficient to identify important factors that affect the management of sedation. The importance of assessment is emphasised and should be carried out by a trained healthcare professional experienced in supporting children and young people undergoing sedation.

The assessment (and other details of sedation management) should be recorded in the healthcare record so that important details are available for any subsequent sedation or anaesthesia. Clear healthcare records may prevent mistakes and reduce risks.

Information and consent

The GDG agreed that each child or young person should be assessed concerning their capacity to make decisions, taking into account their previous experiences, level of maturity and cognitive development. Children and young people who have capacity to consent should be encouraged to do so.

Valid consent should be voluntary, fully informed and the person giving consent should have capacity. Besides their parents or guardians, children and young people might like to know about their illnesses, investigations and treatment and what is likely to happen to them. They should be involved in decisions about their care, even if they are not able to make decisions on their own, and should be given the opportunity to ask questions. It is important that patients are given choice about which sedation technique, if any, should be used. The choice will depend upon the risks, the side effects and the patient's ability to cope with discomfort or anxiety. In essence, the choice is between sedation techniques, no sedation or anaesthesia. There will be local variation within the healthcare settings regarding consent protocols. Department of Health guidance on obtaining consent and what to expect if you are a young person, parent or carer[2-5] is available online at:

http://www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Consent/Consentgeneralinformation/index.htm

Healthcare professionals have a duty to explain fully to the child or young person about the proposed sedation technique and any alternatives. The explanation should be given in a way that the patient can understand and it should be supported by illustrations, or in other formats, and in the language of the patient and family. High quality patient information provision is the cornerstone of good clinical care and is essential for consent to be valid.

Children and young people should be provided with timely, accessible information that is easy to understand and appropriate to their level of understanding and maturity.

Details of consent and relevant discussions should be available in the healthcare record to help any future patient management.

4.1.4 Health economic considerations

An economic analysis was not carried out. The need for assessment is the same for all the sedation techniques considered and it is expected to have a low impact on the NHS resources.

4.1.5 Recommendations on pre-sedation assessment, communication, patient information and consent

Recommendation 1	Ensure that trained healthcare professionals (see section on personnel and training) carry out pre-sedation assessments and document the results in the healthcare record.

Recommendation 2	Establish suitability for sedation by assessing all of the following: - current medical condition and any surgical problems - weight (growth assessment) - past medical problems (including any associated with previous sedation or anaesthesia) - current and previous medication (including any allergies) - physical status (including the airway) - psychological and developmental status.

Recommendation 3	Seek advice from a specialist before delivering sedation: - if there is concern about a potential airway or breathing problem - if the child or young person is assessed as American Society of Anesthesiologists (ASA) grade 3 or greater - for infants, including neonates.

1

Recommendation 4	Ensure that both the following will be available during sedation: - a healthcare professional and assistant trained (see section on personnel and training) in delivering and monitoring sedation in children and young people - immediate access to resuscitation and monitoring equipment (see section on clinical environment and monitoring).

2

Recommendation 5	Choose the most suitable sedation technique based on all the following factors: - what the procedure involves - target level of sedation - contraindications - side effects - patient (or parent or carer) preference.

3

Recommendation 6	To enable the child or young person and their parents or carers to make an informed decision, offer them verbal and written information on all of the following: - proposed sedation technique - the alternatives to sedation - associated risks and benefits.

4

Recommendation 7	Obtain and document informed consent for sedation.

4.1.6 Research recommendation on pre-sedation assessment, communication, patient information and consent

- For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation, what factors should be assessed to both establish the need for sedation and reduce the risk of adverse events?

Why it is important

Some children need sedation, some need anaesthesia, and some need behavioural management alone. There is wide variation in how this choice is made and a recommended standard method of assessment may reduce variation and improve both success and safety of sedation when it is chosen. Furthermore, an assessment tool may prevent unsuitable choices and improve the overall management of procedures in children. The GDG suggest an observational study to determine the important factors, followed by a consensus study to develop a tool. The assessment tool should be tested by a randomised comparison of children and young people who have been assessed routinely with those who have been assessed using the tool. The assessment tool aims to improve sedation success and quality, and reduce any complications.

4.2 Fasting

4.2.1 Clinical introduction

The importance of safety in any clinical procedure is paramount, and in relation to sedation the question 'should a child or young person be fasted before the procedure?' is important. Currently, local policy in relation to the administration of general anaesthesia is shaped by the joint Royal College of Nursing (RCN)/Royal College of Anaesthetists (RCA) Clinical Guideline 'Perioperative Fasting in Adults and Children' (2005)[8]. However, there is acknowledged variation in practice to routine fasting (or not) when applied to the management of children and young people receiving sedation. This guideline is timely in providing standard recommendations for practice.

4.2.2 Clinical methodological introduction

CLINICAL QUESTION:

For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques:

5. Should fasting versus no fasting be implemented to prevent adverse outcomes?

The review for this question consisted of three evaluation processes:

1) The joint RCN/RCA guideline 'Perioperative Fasting In Adults And Children' (2005)[8] was assessed using the AGREE instrument for appraisal of clinical guidelines.

2) The searches in the joint RCN/RCA guideline 'Perioperative Fasting In Adults And Children' (2005)[8] were updated from the last date searched in that guideline (2004) to 2009. The purpose of this search to was to identify recent publications that might impact on recommendations for fasting in paediatric anaesthesia.

3) Since the RCN/RCA guideline did not cover sedation, a full search of the literature relevant to fasting for paediatric sedation was conducted.

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

Population: 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.

Intervention: Fasting before sedation with one of the following drugs: midazolam, ketamine, propofol, chloral hydrate, nitrous oxide, sevoflurane, fentanyl, morphine intravenous or intramuscular, or diamorphine.

Comparison: Fasting versus no fasting.

Outcomes for adverse events as evidenced by:

- Aspiration

- Vomiting
- Oxygen saturation <90%
- Respiratory intervention, including:
    - oral-pharyngeal airway
    - intubation
    - assisted ventilation.

AGREE appraisal

The AGREE instrument was used to appraise the joint RCN/RCA clinical guideline 'Perioperative Fasting In Adults And Children' (2005)[8]. The full instrument with reviewer's comments is available in Appendix I. The overall assessment was as follows:

This guideline is recommended with the following provisos:

- Update searches for the period from 2005 to 2009 are carried out, as the guideline is scheduled for review in 2009.
- Description of consensus methodology used for any Grade D recommendations is described.
- Conflict of interest records for the GDG are summarised.

At the request of the GDG, an update search was carried out for review of perioperative fasting in children and young people (2004-2009). A full search was conducted for fasting for sedation in children and young people for diagnostic and therapeutic procedures.

Perioperative fasting in children and young people (2004-2009)

No RCTs or observational studies were identified in the update search that met the inclusion criteria for a review of fasting in this population in preparation for general anaesthesia.

Fasting for sedation in children and young people (all dates)

One RCT and six observational studies were identified in the search for fasting prior to sedation in this population.

Fasting State and Episodes of Vomiting in Children Receiving Nitrous Oxide for Dental Treatment[133].

This controlled crossover study was performed to determine the frequency of vomiting during nitrous oxide/oxygen administration and to assess the relationship between fasting status and vomiting. A convenience sample of children (n=113) was randomly assigned to be fasting from solids for six hours and clear liquids for two hours before the procedure and their first dental treatment and non-fasting for the second treatment or, alternatively, non-fasting initially and fasting for the next visit. The treatment time was under 35 minutes in all cases. The average fasting time was six hours before treatment in the fasting group and one hour before treatment in the non-fasting group. Vomiting occurred in only one subject, a child who was not fasting (1/113). This was a non-significant result.

The following six studies represent observational data that records the incidence of adverse events related to the fasting status of children undergoing sedation. The data is summarised in Table 1.

Table 1. Adverse events related to pre-sedation fasting status

Author **Study design** **Setting** **Drug**	**Total N** **Age range**	**Adverse events/children fasted per guidelines (%)**	**Adverse events/children not fasted (%)**	**Results**
Agrawal 2003[12] Prospective case series ED, USA Mixed: 47% ketamine 23% fentanyl and midazolam 24% chloral hydrate and pentobarbital	905 5 days –18 years Median age: 5.4 years	32/396 (8.1%) total adverse events	35/509 (6.9%) total adverse events	No association between fasting state and adverse events. All adverse events were minor. Emesis occurred in 15 (1.5%) patients. There were no episodes of aspiration.
Babl 2005[23] Prospective case series Emergency Department, Australia 50–70% nitrous oxide	218 14 months – 17 years Median age: 8 years 3 months	4/63 (6.3%) vomiting	11/155 (7.1%) vomiting	There were no serious adverse events and no episodes of aspiration. The adverse events recorded represent emesis, which occurred in 15 children in total. There was no significant association between preprocedural fasting and emesis in this series.
Heistein 2006[92] Retrospective review Echocardiography, USA Chloral hydrate	1095 1 month -3 years			Multivariate analysis showed that fasting times (0.6-72 hours) were not significantly associated with adverse events (p=0.36) including apnea, airway obstruction, hypoxia, hypercarbia, hypotension, vomiting and prolonged sedation.

Author Study design Setting Drug	Total N Age range	Adverse events/children fasted per guidelines (%)	Adverse events/children not fasted (%)	Results
Keidan 2004[128] Retrospective review Auditory brainstem response, Israel Chloral hydrate, 50-60 mg/kg	200 infants (mean age 16 months ± 10 in Group A – fasted group and mean age 14 months ± 13 in Group B – not fasted group)	3/100 transient desaturation 25/100 prolonged sedation (>120 minutes) 2/100 agitation 0/100 vomiting 21/100 failure to achieve adequate sedation with first dose	1/100 transient desaturation 5/100 prolonged sedation (>120 minutes) 0/100 agitation 0/100 vomiting 11/100 failure to achieve adequate sedation with first dose	The fasted group showed significantly higher failure rate to achieve sedation with first dose (p=0.03) and hence needed higher doses (p<0.01) and were sedated for longer periods p<0.001). No difference was found in the adverse effect rate.
Roback 2004[190] Prospective cohort Emergency Department, USA Ketamine, midazolam and 53/2085 'other' drugs	2085 19 days -18 years Median age: 6.7 years	Fasted 2-4 hours: Respiratory (apnea, laryngospasm, oxygen saturation <90%): 30/391 (7.7%) Vomiting: 40/391 (10.2%) Fasted 4-6 hours: Respiratory (apnea, laryngospasm, oxygen saturation <90%): 31/430 (7.2%) Vomiting: 10/150 (6.7%) Fasted 6-8 hours: Respiratory (apnea, laryngospasm, oxygen saturation <90%): 7/281 (9.6%) Vomiting: 18/281 (6.4%) Fasted >8 hours: Respiratory (apnea, laryngospasm, oxygen saturation <90%): 19/303 (6.3%) Vomiting: 27/303 (8.9%)	Fasted 0-2 hours: Respiratory apnea, laryngospasm, oxygen saturation <90%): 11/150 (7.3%) Vomiting: 30/430 (7.0%)	No significant differences were found in adverse events according to fasting times. No patients experienced clinically apparent aspiration.

Author Study design Setting Drug	Total N Age range	Adverse events/children fasted per guidelines (%)	Adverse events/children not fasted (%)	Results
Treston 2004[217] Prospective cohort Emergency Department, Australia Ketamine	257 1-12 years	Longer than 3 hours: 20/127 (15.7%) vomited	2-3 hours: 14/100 (14%) vomited 1 hour: 2/30 (6.6%) vomited	There was a non-significant trend to increased incidence of vomiting with increased fasting times ($p=0.08$)

Other relevant publications

The Dental Clinical Guidance for conscious sedation in dentistry was published in 2006[45] and highlighted fasting before conscious sedation as an area requiring further high-quality research.

Another prospective cohort study in which children were sedated for gastroscopy with demerol or diazepam showed that there was no significant correlation between duration of fasting from fluids and solids from 0.5 to 24 hours and either gastric volume or pH[100].

4.2.3 GDG discussion on fasting

When considering what guidance should be provided in relation to fasting, the GDG looked at a range of possible recommendations. This ranged from no fasting is necessary prior to administration of sedation through to the application of standard fasting policy throughout the UK shaped by the joint RCN/RCA clinical guideline 'Perioperative Fasting In Adults and Children' (2005)[8], known colloquially as the "2-4-6" rule, namely 2 hours for clear fluid, 4 hours for breast milk and 6 hours for solids (including formula milk). This guideline was positively appraised as per NICE Technical Manual (2009)[172] using the AGREE instrument, and the initial GDG position was to apply standard fasting policy.

During GDG discussion two main concerns emerged; these were that children and young people undergoing sedation should not be unnecessarily fasted and the importance of safety. One pharmacological intervention, nitrous oxide alone (up to 50% in oxygen), was felt to have no safety concerns and on this basis the GDG accepted that recommendations should reflect this. Given the publication date of the RCN/RCA guideline[8], the original search strategy was re-run to the end of 2009, with an additional search applied to the target population of this guideline: children and young people receiving sedation and not general anaesthesia. While a number of studies were found, the quality of the evidence was weak, with the GDG choosing to apply the standard fasting recommendation from the Clinical Guideline 'Perioperative Fasting in Adults and Children' (2005)[8]. The wording of the recommendation that focuses on 'elective procedures', reflects an important GDG discussion on administering sedation for emergency procedures. Clinical decision making in this context was recognised to balance the risks and benefits of sedation. The GDG noted that the fasting status of a child presenting in the emergency context cannot be guaranteed and recognised the importance of local clinical decision making given the clinical circumstances. It was also noted by the GDG that recording pre-sedation fasting was important and should be inserted into the healthcare record.

4.2.4 Health economic considerations

An economic analysis was not carried out. It was anticipated that fasting will not significantly increase the healthcare resources required to manage a patient undergoing a procedure.

4.2.5 Recommendations on fasting

Recommendation 8	Before starting sedation, confirm and record the time of last food and fluid intake in the healthcare record.

Recommendation 9	Fasting is not needed for: - minimal sedation - sedation with nitrous oxide and oxygen - moderate sedation during which the child will maintain verbal contact with the healthcare professional.

Recommendation 10	Apply the 2-4-6 fasting rule[§§] for elective procedures using any sedation technique other than those in recommendation 1.2.2 (that is, for deep sedation and moderate sedation during which the child might not maintain verbal contact with the healthcare professional).

Recommendation 11	For an emergency procedure in a child or young person who has not fasted, base the decision to proceed with sedation on the urgency of the procedure and the target depth of sedation.

4.2.6 Research recommendation on fasting

- For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation how long should they be fasted to prevent adverse events?

Why it is important

Inhalation of gastric contents can be fatal. Loss of consciousness is associated with the loss of vital airway reflexes and inhalation of gastric contents is possible. Consequently, fasting (in order to keep the stomach empty) is standard practice before general anaesthesia and has become standard before any sedation technique that may cause loss of consciousness. Prolonged fasting, however, is distressing and can cause dehydration and hypoglycaemia. It would be helpful to know the minimum length of time necessary to fast a child before sedation in order to ensure that the stomach is empty, and to know that likelihood of regurgitation or vomiting is very small.

[§§] Fasting times should be as for general anaesthesia:

- 2 hours for clear fluids
- 4 hours for breast milk
- 6 hours for solids.

4.3 Psychological preparation

For a full narrative review on psychological preparation see chapter 5.

4.3.1 Clinical introduction

A substantial body of research from different paradigms affirms that children who have been repeatedly exposed to anxiety-provoking painful medical events are at increased risk for developing adult dysfunctional cognitions and avoidant attitudes toward healthcare. In some cases, serious mental health problems, such as post-traumatic stress, can occur. The pharmacological management of acute pain and anxiety in children undergoing therapeutic and diagnostic procedures outside the operating room has developed substantially in the past 15 years and procedural sedation is frequently used for the care of children in many medical settings. Pharmacological sedation and analgesia, however, do not adequately address the emotional, cognitive, and behavioural components that are integral to the sedation experience. Consequently, effective patient management requires an interdisciplinary approach and should include psychological techniques, which can be used alone or in combination with pharmacological treatment.

4.3.2 Clinical methodological introduction

CLINICAL QUESTION:

For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques:

6. what standard psychological preparation, coping skills and strategies should be used?

Population: 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.

Intervention: Psychological preparation.

Comparisons:

- No intervention, usual care
- Pre-medication
- Another non-pharmacological treatment

Outcomes for efficacy of psychological preparation:

- Completion of procedure
- Behavioural ratings including:

    - pain as assessed using validated pain scales, such as FACE or VAS
    - children's Hospital of Eastern Ontario Pain Scale (CHEOPS), Spielberger State-Trait Anxiety Inventory (STAI)
    - procedural distress as assessed by validated scales such as Observational Scale of Behavioural Distress (OSBD)
    - parent/patient satisfaction
- Sedation timing including:
    - length of induction (defined as time from administration of sedation drug to initiation of procedure)
    - 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, that is, induction for anaesthesia and medical procedures (see chapter 5).

4.3.3 Clinical evidence statements

The effects of a psychological preparation program on anxiety in children and adolescents undergoing gastrointestinal endoscopy; Mahajan 1998[155].

This study was carried out at the Cleveland Clinic in the USA in a population of children and young people ages 6-19 years. In a sample of 60 patients, the control group received usual patient education and the intervention group received psychological preparation consisting of demonstration of materials that would be used in the procedure. A doll was used as a model, if age appropriate. A book with photographs of a child undergoing the procedure was also shown. The same child life specialist provided all of psychological preparation.

In this study, the outcomes of anxiety and distress were measured using validated scales. The Speilberger State-Trait Anxiety Inventory (STAI) was administered to patients after the psychological intervention but before the endoscopic procedure. The Observational Scale of Behavioural Distress (OSBD) was administered during the procedure.

Compared to usual care the children receiving psychological preparation had significantly less anxiety before the procedure [low quality evidence].

There was no significant difference between the groups in distress levels as measured by the OSBD instrument, although patients in the intervention group had a lower weighted mean score interval (1 versus 1.3).

Author(s): Mahajan 1998[155]

Question: Should psychological preparation versus usual care be used for paediatric sedation?

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological preparation	Usual care	Relative (95% CI)	Absolute		
Anxiety (range of scores; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD -10.10 (-13.77 to -6.43)	LOW	
Distress (range of scores; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD -0.30 (-0.88 to 0.28)	LOW	

1 Method of randomisation and allocation not described. Blinding of assessors not described.
2 Small study with 30 participants in each group. Outcome measures dependant upon subjective perception of anxiety and distress despite validation.

Anticipatory anxiety in children visiting the dentist: lack of effect of preparatory information; Olumide 2009[175]

This study was carried out at the Kings College Hospital paediatric dental clinic, London, in a population of children aged 8-12 years. In a sample of 50 patients, the intervention group received a preparatory leaflet and the control group received a leaflet about healthy eating. Anxiety levels were measured using the Facial Image Scale before and after children read their leaflets. Intra-group comparisons were made. No inter-group statistics were calculated

In both groups there was no significant difference in anxiety levels before or after reading the leaflets [moderate quality evidence].

Author(s): Olumide 2009[175]
Question: Should preparatory leaflet be used for anxiety?
Settings: dental treatment

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preparatory leaflet	control	Relative (95% CI)	Absolute		
Anxiety with preparatory leaflet (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	25	25	-	MD 0.56 (0.08 to 1.04)	MODERATE	
Anxiety with healthy eating leaflet (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.24 (-0.16 to 0.64)	MODERATE	

1 Although sample size calculations were acceptable for 80% power, this remains a small study and should be repeated in larger population.
2 No explanation was provided.

4.3.4 GDG discussion on psychological preparation

The GDG noted that sedation is only one of the management options available for children and young people undergoing therapeutic or diagnostic procedures. Psychological interventions can be used to reduce anxiety and manage behaviour in combination with sedation.

Parental involvement in the preparation of the child and during the procedure may reduce the distress caused by separation anxiety, particularly in young children.

The GDG believe psychological techniques (for example, information for the patient/carer before, during and after sedation, cognitive behavioural therapy, distraction, guided imagery, hypnosis, demonstration play therapy and music therapy) form part the child/family preparation. An individualised approach to using these techniques will benefit the child and minimise fear, anxiety, pain and distress.

In making the recommendations, the GDG agreed that healthcare professionals involved in sedation should:

- have knowledge and understanding of psychological methods of patient preparation and coping skills and strategies, such as the "tell-show-do" method, and simple distraction techniques
- consider psychological techniques for the child and family as part of patient preparation and tailor to the age, understanding and needs of the child/parent
- involve the parent/carer in the preparation of the child and during the procedure
- offer factual information about the clinical setting, the procedure itself and the different steps of the procedure
- offer information and discussion about what the child may experience before, during and after the procedure
- discuss coping strategies and skills with the child/family
- consider using trained psychosocial professionals for patient preparation
- modify psychological methods of preparation according to the urgency of the procedure.

4.3.5 Health economic considerations

An economic analysis was not conducted. Preparation for children and young people undergoing diagnostic and therapeutic procedures under sedation techniques was felt to be part of routine care. Providing patients and their families with information on coping strategies was felt to be part of a routine care.

4.3.6 Recommendations on psychological preparation

Recommendation 12	Ensure that the child or young person is prepared psychologically for sedation by offering information about: - the procedure - what the child or young person should do and what the healthcare professional will do - the sensations associated with the procedure (for example, a sharp scratch or numbness) - how to cope with the procedure.

Recommendation 13	Ensure that the information is appropriate for the developmental stage of the child or young person and check that the child or young person has understood the information.

Recommendation 14	Offer parents and carers the opportunity to be present during sedation if appropriate. If a parent or carer decides to be present, offer them advice about their role during the procedure.

Recommendation 15	For an elective procedure, consider referring to a mental health specialist children or young people who are severely anxious or who have a learning disability.

4.3.7 Research recommendation on psychological preparation

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures under sedation what psychological techniques can lead to sedation sparing, improve patient/family satisfaction and ensure safe completion of the procedure?

Why it is important

Psychological interventions in children and young people are used extensively in combination with pharmacological interventions for the management of painful medical procedures and for pre- and post-operative distress and pain management after anaesthesia. Similar data are lacking for children undergoing diagnostic and therapeutic procedures under sedation. However, a significant body of literature shows sedation sparing, reduced incidence of side effects and increased satisfaction in adults undergoing various procedures under sedation when combined with psychological interventions such as hypnosis. Randomised controlled trials testing the efficacy of the combination of psychological interventions with sedation versus sedation on its own will allow us to determine whether adding psychological interventions to patient management under sedation is beneficial for children and young people.

4.4 Personnel and training

4.4.1 Clinical introduction

All healthcare professionals involved in the care of sedated children and young people should be appropriately trained. The training of healthcare professionals delivering sedation currently varies by speciality. There are a number of reports that provide guidance on the types of training courses available (for example "Conscious Sedation in the Provision of Dental Care"[208]) but there remains significant variability between different healthcare providers and specialities.

The aim of this section is to provide clear advice on training requirements to ensure that every healthcare professional is competent in the sedation techniques they use and in the management of complications that might arise when using these techniques. This is important because there is currently no uniform requirement for assessing sedation skills, nor any consistent requirement for revalidation of skills.

Training may be delivered by Trusts, Universities, Royal Colleges or other independent providers but the responsibility for ensuring that healthcare professionals have undergone appropriate training should lie with the local NHS Trust providing sedation services.

4.4.2 Clinical methodological introduction

CLINICAL QUESTIONS:

For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation:

7. what generic and specific skills are required for different team members and for different levels of sedation?

8. what training and competences are required for the personnel involved?

9. what assessment and maintenance of skills is required for the personnel involved?

GDG sought to provide guidance to these questions based on their expert experience and opinion.

4.4.3 GDG discussion on personnel and training

Skills required for sedation

The GDG agreed that sedation should be administered by a team and someone in the team should have the skills to ensure the sedation is effective and that any complications are managed successfully. Many types of skills were discussed, including pre-sedation patient assessment and communication. During sedation until the end of recovery the skills of observation and monitoring were considered to be essential for safety. These include airway patency, breathing rate and depth, pulse, pallor and cyanosis and depth of sedation. The complications of airway obstruction and respiratory arrest can be readily overcome by prompt recognition and management; if they occur, serious consequences should be unlikely. These skills need to be practised regularly. The skills for the management of cardiac arrest are also essential.

Training and competencies

The GDG agreed that all healthcare practitioners administering sedation need to be trained in the practice of delivering effective sedation. Since there are a number of sedation techniques, the training and competencies would need to be specific to the sedation technique. Some generic skills were agreed, such as the assessment of conscious level and pain. In respect to the complications of sedation, however, the GDG accepted that some sedation techniques were not safe enough to be used unless healthcare practitioners had specific training. They would need to be trained to manage the complications of that technique. If airway or respiratory complications were considered to be extremely unlikely, then some skills may be considered unnecessary. The recommendations took account of the likelihood of airway and respiratory complications of the sedation according to the technique and the target level of sedation.

Techniques with a narrow margin of safety readily cause airway obstruction and apnoea. Consequently, the GDG believed that these drugs could only be recommended for use by teams with special expertise. This situation applies to most anaesthetic agents and also the use of some combinations of drugs with opioids. The risk of opioids relates to judging the correct dose to overcome the pain. If the pain reduces (for example after the extraction of a tooth) the opioid causes the respiratory depression and this is made more likely if the patient is deeply sedated.

The GDG noted it is essential that healthcare practitioners undergo competency-based assessment upon completion of training to ratify their ability to undertake sedation on children and young people. Current practice varies between providers and specialities and there is currently no uniform requirement for assessing sedation skills, nor any consistent requirement for healthcare practitioners to revalidate their skills.

Assessment and maintenance of skills

The GDG pointed out that there are a number of reports that have provided guidance on the nature of training but there remains variability across different healthcare providers and specialities.

The GDG considered the following in making recommendations by consensus:

- Healthcare professionals practising sedation should have documented evidence of competency. This should include:
    - satisfactory completion of knowledge-based learning (for example, certificate confirming completion of a didactic training course covering the theoretical principles of sedation practice)
    - log/record of satisfactory acquisition of practical and clinical skills relevant to the type of sedation being used including:
        - log-record of patients managed under supervision
        - a record of successful completion of work-based assessments (for example, Direct Observation of Procedural Skills - DOPS)

- Healthcare practitioners who have already completed specialist training should attend a didactic training course to ensure up-to-date knowledge and should be able to demonstrate a track record of safe sedation practice in the techniques they use.

- Healthcare professionals practising sedation should keep their skills up-to-date by regular practice of sedation techniques and reinforcement of theoretical and practical skills, undertaken as an essential component of Continuing Professional Development.

- Healthcare professionals should maintain documentary evidence of clinical activity and Continuing Professional Development in sedation.

Failure of sedation

Sedation may not always succeed; the drugs may not be effective enough at the desired target level of sedation. If a patient becomes too distressed and cannot cope or cooperate with a painful procedure, increasing the doses of sedation drugs may only be effective if they cause deep sedation or anaesthesia. Likewise, if sedation does not cause a child to sleep during painless imaging, increasing the doses may only be effective if the child becomes unconscious. Deep sedation techniques often cause a prolonged recovery time and have the associated hazards of suppression of vital airway and breathing reflexes. In these circumstances anaesthesia drugs are more suitable because they can be given in the dose required to cause the sedation level that the patient needs. Moreover, they are short-acting drugs and can be given to cause sedation or anaesthesia over the period of the procedure; they do not cause prolonged recovery times. If the healthcare professional is suitably trained and has the facilities for anaesthesia, anaesthesia is feasible as soon as the patient needs it. Often, the skills and facilities are not available and anaesthesia will need to be arranged at another time and place.

4.4.4 Health economic considerations

An economic analysis was not carried out. The cost of training healthcare professionals is not normally considered within cost-effectiveness analysis but may be included in the budget impact analysis.

1 ### 4.4.5 Recommendations on personnel and training

Recommendation 16

Healthcare professionals delivering sedation should have knowledge and understanding of and competency in:

- sedation drug pharmacology and applied physiology

- assessment of children and young people

- monitoring

- recovery care

- complications and their immediate management, including paediatric life support.

2

Recommendation 17

Healthcare professionals delivering sedation should have practical experience of:

- effectively delivering the chosen sedation technique and managing complications

- observing clinical signs (for example airway patency, breathing rate and depth, pulse, pallor and cyanosis, and depth of sedation)

- using monitoring equipment.

3

Recommendation 18

Ensure that members of the sedation team have the following life support skills:

	Minimal sedation*	Moderate sedation	Deep sedation
All members	Basic	Basic	Basic
At least one member		Intermediate	Advanced

* including sedation with nitrous oxide alone (in oxygen) and conscious sedation in dentistry.

4

Recommendation 19

Ensure that a healthcare professional trained in delivering anaesthetic agents (see appendix J) is available to administer:

- sevoflurane[***]

- propofol[†††‡‡‡],

- opioids[§§§] combined with ketamine[****††††].

Recommendation 20

Healthcare professionals delivering sedation should have documented up-to-date evidence of competency including:

- satisfactory completion of a theoretical training course covering the principles of sedation practice

- a comprehensive record of practical experience of sedation techniques, including details of:

  - sedation in children and young people performed under supervision
  - successful completion of work-based assessments.

[***] Sevoflurane is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) sevoflurane did not have UK marketing authorisation for this indication. See appendix J.

[†††] Propofol is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) propofol did not have UK marketing authorisation for this age group. See appendix D.

[‡‡‡] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.

[§§§] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.

[****] Ketamine is a dissociative agent: the state of dissociative sedation cannot be readily categorised as either moderate or deep sedation; the drug is considered to have a wide margin of safety.

[††††] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.

Recommendation 21	Each healthcare professional and their team delivering sedation should ensure they update their knowledge and skills through programmes designed for continuing professional development.

Recommendation 22	Consider referring to an anaesthesia specialist a child or young person who is not able to tolerate the procedure under sedation.

4.4.6 Research recommendation on personnel and training

- 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?

Why it is important

Potent drugs can cause unintended airway obstruction. Anaesthetists are skilled at managing airway obstruction because they practise this regularly. However, anaesthetists are a scarce resource so non-anaesthetists need to learn how to manage airway obstruction. The skills that are needed have been identified but can these skills be attained and maintained by professionals who need them occasionally? The GDG suggests that a standard teaching method and assessment tool are developed. This would involve an observational study of a cohort of trainees, who can be assessed, trained and then reassessed at varying intervals to determine whether the training is successful and how often it is necessary.

4.5 Clinical environment and monitoring

4.5.1 Clinical introduction

Sedation of children and young people happens in a variety of clinical environments, with a range of specialty staff, and a selection of different sedative agents.

Sedation carries a risk of serious adverse events, including hypoxia, reduced consciousness, apnoea and loss of airway control. In some sedation techniques the sedation level can become deep rapidly, so, in order to ensure their safety, it should be possible to monitor a child or young person for a deeper level of sedation than planned.

Assessment of requirements for monitoring should be undertaken prior to any sedation event, and monitoring should start prior to administration of any sedation agent. Monitoring will depend not only on sedation technique but also the child's tolerance, and may become less intrusive as the child becomes more awake.

This section makes recommendations for minimum levels of monitoring for all children and young people receiving sedation, to reduce the risk of adverse events, and improve patient safety.

4.5.2 Clinical methodological introduction

CLINICAL QUESTIONS:

For children and young people under the age of 19 undergoing diagnostic and therapeutic procedures under sedation techniques:

10. during moderate or deep sedation techniques, what monitoring and equipment is required to reduce the risk of complications?

11. when should monitoring stop?

GDG sought to provide guidance to these questions based on their expert experience and opinion.

4.5.3 GDG discussion on clinical environment and monitoring

What monitoring is required?

The GDG aimed to provide consistency in monitoring standards, to provide some evidence around the use of capnography, to inform judgement and to reduce the risk of adverse events to patients.

The GDG noted that monitoring varies across specialties. When nitrous oxide alone is used, for example for dental treatment, the GDG stated that monitoring as recommended for other sedative drugs is not needed. In emergency care, monitoring commences prior to sedation. Vital signs are taken prior to commencement and documented at intervals throughout the procedure. The healthcare team's approach in determining frequency of observation/monitoring interventions is dependant on the procedure itself, the level of sedation to be achieved and child's tolerance. The GDG indicated that in some sedation techniques the sedation level can become deep rapidly and monitoring should be increased if patient becomes unrousable or unconscious.

The GDG noted that patient monitoring needs to begin prior to administration of the agent(s) unless this causes unnecessary distress. The GDG described sedation monitoring as a continuum from awake to anaesthesia, which becomes less intrusive as the child becomes more awake.

The GDG raised concern about the difficulty in dealing with monitoring of children who are uncooperative, distressed or anxious, as well as on the lack of understanding of the potential effects/side-effects of drugs used and the risks of a changing target state. This concern reflects the range of possible behaviours and compliance observed in practice and the various techniques that healthcare professionals may apply in effectively managing this. Factors for consideration are seen in the recommendation and provide direction for the sedation team.

When should monitoring stop?

The GDG noted that practitioners do sometimes take their 'eye off the ball' when the procedure is complete, but the child is still sedated. The GDG agreed, by general consensus, that the point at which monitoring stops is not the same as discharge criteria as sedation state may vary throughout the recovery period.

Staff and facilities should be available to manage an unconscious or an acutely sick patient until either they have recovered or they can be transported to another facility who can continue their care.

4.5.4 Health economic considerations

An economic analysis was not carried out. The appropriate monitoring will be largely determined by safety considerations. If the use of a particular sedation technique increases the duration and intensity of monitoring, then this should have been captured in the cost estimate of that sedation technique. We have included the cost of staff and consumables associated with different sedation techniques in our economic analysis.

4.5.5 Recommendations on clinical environment and monitoring

Recommendation 23	For moderate sedation excluding with nitrous oxide alone (in oxygen) continuously monitor, interpret and respond to changes in all of the following: - depth of sedation - respiration - oxygen saturation - heart rate - pain - coping - distress.

Recommendation 24	For deep sedation continuously monitor, interpret and respond[a] to changes in all of the following: - depth of sedation - respiration - oxygen saturation - heart rate - three-lead electrocardiogram - end tidal CO2 (capnography)[b] - blood pressure (monitor every 5 minutes)[b] - pain - coping - distress. [a]For deep sedation, the healthcare professional administering sedation should be involved only in continuously monitoring, interpreting and responding to all of the above [b]End tidal CO_2 and blood pressure should be monitored, if possible, provided that monitoring does not cause the patient to awaken and so prevent completion of the procedure

Recommendation 25	Ensure that data from continuous monitoring during sedation are clearly documented in the healthcare record.

Recommendation 26	After the procedure, continue monitoring until the child or young person: - has a patent airway - shows protective airway and breathing reflexes - is haemodynamically stable - is easily roused.

4.5.6 Research recommendations on clinical environment and monitoring

- Which depth of anaesthesia monitors can be used to monitor depth of sedation in children and which is best?

Why it is important

Several depth of anaesthesia monitors are in use around the world. Most use processed EEG signals while some use stimulation of the brainstem by auditory stimuli. It is not yet clear whether the available monitors can follow children through different levels of sedation accurately and this study would set out to determine which monitor best tracks the transition from moderate to deep sedation in children of different ages.

4.6 Discharge criteria

4.6.1 Clinical introduction

The aim of establishing discharge criteria is to ensure children go home from a sedation event only when it is safe for them to do so. Recovery from sedation is a continual process and some children might benefit from a longer period of less-intense observation before being discharged. This is particularly important when using sedation agents that have a prolonged effect and may delay a child's complete recovery, or pose the risk of re-sedation.

4.6.2 Clinical methodological introduction

CLINICAL QUESTION:

For children and young people under the age of 19 after diagnostic and therapeutic procedures under sedation techniques

12. what discharge criteria are required?

The GDG sought to provide guidance to this question based on their expert experience and opinion.

4.6.3 GDG discussion on discharge criteria

The GDG noted that in current practice discharge criteria vary across specialties and professionals. In emergency care, children will be observed/monitored until they reach a 'pre-sedation' state. They are discharged into the care of a responsible adult, and advice is given on what to expect in the first 24 hours after sedation. Recovery from both the procedure and the sedation takes a variable length of time and depends upon the procedure, its length, the sedation technique and the doses used.

A simple checklist can be used to make sure that children have returned to their pre-sedation states. However, this should also take into account the capabilities of the person caring for the child following discharge, the presence of other medical problems and the distance the family has to travel to obtain medical assistance. It is more important to individualise the times of discharge rather insist on a minimum length of stays.

Recovery from sedation caused by some drugs and techniques can be prolonged and unpredictable and there is a risk that after discharge the patient may become re-sedated. In this situation there may be a danger of respiratory depression and hypoxia. Prolonged sedation may also mean that intake of drink and food may be delayed, leading to dehydration and hypoglycaemia. These problems may be more common with orally administered drugs because absorption can be delayed and unpredictable.

4.6.4 Health economic considerations

An economic analysis was not carried out. The choice of discharge criteria should be based on minimizing the risk that a patient will experience an adverse event after discharge. If the use of a particular sedation technique results in the patient taking longer to meet the discharge criteria, and is associated with increased duration of stay, this should have been accounted for in the costing of the technique. We have included the cost of recovery in our costing of sedation techniques.

4.6.5 Recommendation on discharge criteria

Recommendation 27	Ensure that all of the following criteria are met before the child or young person is discharged: - vital signs (usually body temperature, heart rate, blood pressure and respiratory rate) have returned to normal levels - the child or young person is awake (or returned to baseline level of consciousness) and there is no risk of further reduced level of consciousness - nausea, vomiting and pain have been adequately managed.

5 Psychological preparation

5.1 Narrative review

5.1.1 Introduction

This narrative review provided material to inform the GDG and to enable consensus decisions leading to recommendations on how children and young people should be prepared prior to their sedation experience. The nature of the evidence base in this area lends itself to this approach.

A full literature search was conducted for psychological preparation for sedation in children. The search was not limited by study design. The resulting 1455 studies were double sifted by the research fellow and by the reviewer for this topic. Two hundred and eight studies were ordered and quality assured by the reviewer.

The benefits of a systematic narrative review of the clinical evidence are highlighted by Oxman[176] and colleagues. Applying the quality assurance principles advocated by Oxman[176], a valid review article can provide the best possible source of information that can lay a foundation for clinical decisions to be made. There is an argument that focused narrative reviews for these important areas of preparation and assessment of the child prior to sedation are more likely to provide valid results that are useful for clinicians. Having provided the background and context for this review, we begin by defining psychological preparation and stating its aims and factors that affect its exact nature and content. This is followed by summarising the evidence for the efficacy of psychological preparation for anaesthesia induction and other medical procedures. Following this, the literature regarding parental and children's desire for information is reviewed. Next, the evidence regarding the effects of parental presence during anaesthesia induction and other medical procedures is discussed, along with the role that parents play when present. The review concludes by summarising the existing evidence and good clinical practice and making recommendations for the preparation of children and their parents for sedation.

5.1.2 What is psychological preparation

Psychological preparation includes specific interventions to provide information and reduce anxiety. Providing three types of information is central: (a) information is provided about the procedure itself (that is, steps that children must perform and steps that healthcare professionals will perform); (b) the sensations the patient can expect to feel (for example, sharp scratch, numbness); and (c) about how to cope with the procedure[142].

The aim of pre-sedation and/or preprocedure psychological preparation in children and young people is to:

- reduce anxiety for patients and their parents
- improve patient cooperation
- enhance patient recovery
- increase self-control for patients and their parents
- improve long-term emotional and behavioural adjustment in patients and their parents.

The factors affecting pre-sedation and/or preprocedure preparation are (Kain and Caldwell-Andrews, 2005)[103]:

- the developmental stage of the child or young person
- previous medical experiences
- timing relative to the procedure
- temperament, current anxiety levels and coping style
- role of parents.

There is limited evidence regarding the best way to prepare children and young people for sedation; therefore, the extensive related literature on preparation for painful medical procedures and anaesthesia was reviewed and the results of this body of knowledge informed the present recommendations. Overall, published evidence supports the view that good preparation results in improved sedation outcomes (e.g. less distress and improved adjustment for the parent and patient[139,158]. A number of studies have shown that adequate preprocedural preparation can also reduce anxiety and procedural pain for a range of medical events, including venipuncture[130], dental procedures[166], surgery[103] and voiding cystourethrography[209].

5.1.3 Psychological preparation for anaesthesia induction

Children have numerous concerns related to anaesthesia and surgery including fear of separation, fear of physical harm, fear of the unknown, fear of death, fear of losing control and uncertainty of the limits of acceptable behaviour[79,195]. It has been estimated that 50% - 75% of children undergoing surgery will develop extreme anxiety and distress during the perioperative period[122]. Anxiety experienced by children at induction is associated with distress on awakening in the recovering area and with later postoperative behavioural problems[230]. Younger age, behavioural problems with previous healthcare attendances, longer duration of procedure, having more than five previous hospital admissions and anxious parents at induction are associated with high anxiety at induction[50]. Interestingly, mother's prediction of uncooperative behaviour is a good predictor of anxiety during induction[154]. Of all children undergoing general anaesthesia and surgery, 54% exhibit new onset maladaptive behavioural responses including general anxiety, night-time crying, enuresis, separation anxiety, eating disturbances, sleep-related problems and temper tantrums at 2 weeks postoperatively[105,113,121].

Behavioural preoperative preparation has been advocated in the psychological and medical literature as a way to ameliorate children's preoperative anxiety and facilitate post procedure recovery. An estimated 78% of all major hospitals offer such programmes to children and their parents. These preparation programmes may provide narrative information, an orientation tour, role rehearsal using dolls, a puppet show, child life preparation or the teaching of coping and relaxation skills to children and their parents. Although there is a general consensus about the desirability of these programmes, recommendations regarding the content of preoperative preparation for children differ widely. O'Byrne and colleagues[174] asked a panel of psychological experts to rate the effectiveness of behavioural preparation programs used in the United States prior to surgery. Experts rated each program on a 1 (least effective) to 9 (most effective) Likert scale. Coping skills instruction was ranked as the most effective preoperative intervention, followed by modelling, play therapy, operating theatre tours and printed materials.

Kain and Caldwell-Andrews[103] suggest that a number of variables are important to consider when designing a preparation programme, including child age, timing relative to surgery and the child's previous hospitalisation history. For example, participation in a preparation programme more than 5-7 days prior to surgery has been found to be most beneficial for children 6 years and older, and the least the beneficial timing was when the program is given 1 day before surgery[115,167,193]. Previous hospitalisation history can also be a particular challenge for designing a preparation programme[103]. Information about what to expect on the day of surgery does not offer new knowledge to these children[65] and it has also been demonstrated that simple modelling and play programmes are not beneficial for children with previous hospitalisations. Individualized coping skills training in combination with actual practice have been identified as strategies that are more helpful for these children[116]. Kain and Caldwell-Andrews[103] suggest that the latter types of programs should be designed with the child's specific past experiences in mind.

5.1.4 The benefit of preoperative anxiety reduction programmes – what the evidence says

- Kain and colleagues[110] in an RCT compared three types of behavioural preoperative preparation programmes including a tour of the OR (information based), an information-based + modelling-based programme (OR tour + commercially available videotape) or an information- + modelling- + coping-based programme (OR tour + videotape + child life preparation) with 75 children aged 2-12 years. Children and parents who received child life coping skills preparation exhibited less anxiety immediately following the preparation in the holding area on the day of surgery and on separation to the OR than children and parents who did not receive this preparation. There were no significant differences in anxiety levels across the groups during anaesthetic induction, in the recovery room or at 2 weeks following the operation.

- Golan, Tighe, Dobija, Perel and Keidan[78] found that the use of preoperative medically trained clowns for children undergoing surgery can significantly alleviate preoperative anxiety. In a randomised, controlled and blinded study conducted with 3-8 year olds undergoing GA for elective outpatient surgery, patients were assigned to three groups: Group 1 did not receive midazolam or clown presence (N=22), Group 2 received 0.5mg/kg oral midazolam 30min before surgery up to a maximum of 15mg (N=22), and Group 3 had two specially trained clowns (N=21) present upon arrival to the preoperative holding area and throughout operating theatre entrance and mask application for inhalation induction of anaesthesia. The intervention lasted approximately 20 minutes and the clowns used developmentally appropriate techniques, such as magic tricks, gags, music, games, puppets, word games and bubbles. In all groups parents were present. All children in the study were videotaped in the holding area until the induction of anaesthesia and blinded evaluators used the tapes to rate children's anxiety. The clown group had a statistically significant lower modified-Yale Preoperative Anxiety Scale score (m-YPAS; Kain, Mayes, Cicchetti et al., 1997[117]) in the preoperative holding area compared to a control and a midazolam group. The clowns' effect on anxiety reduction continued when the children entered the operating theatre but was equal at this point to the midazolam group. Upon application of the anaesthesia mask no statistically significant differences were detected between groups, but the clown group had the largest increase in m-YPAS score, which surpassed the other two groups' m-YPAS scores.

- Kain, Caldwell-Andrews, Krivutza, Weinberg, Gaal and colleagues[104] compared the effectiveness of an interactive music intervention and midazolam in alleviating preoperative anxiety in 123 children aged 3-7 years old. The results of this study suggested that interactive music therapy may be useful in alleviating preoperative anxiety on separation from parents and entrance to the OR, but that music therapy did not appear to alleviate children's anxiety at anaesthetic induction.

- Kain and colleagues[108] randomly assigned 408 children and their parents to one of four groups: (1) control, which received standard of care; (2) parental presence, which received standard parental presence during induction of anaesthesia; (3) ADVANCE: received standard-of-care treatment plus multicomponent family-centred behavioural preparation (anxiety-reduction, distraction, video modelling and education, adding parents, no excessive reassurance, coaching, and exposure/shaping); and (4) oral midazolam. Parents and children in the ADVANCE group exhibited significantly lower anxiety in the holding area as compared with all three other groups (34.4 ± 16 vs. 39.7 ± 15; $p=0.007$) and were less anxious during induction of anaesthesia as compared with the control and parental presence groups (44.9 ± 22 vs. 51.6 ± 25 and 53.6 ± 25, respectively; $p=0.006$). Anxiety and compliance during induction of anaesthesia was similar for children in both the ADVANCE and midazolam groups (44.9 ± 22 vs. 42.9 ± 24; $p=0.904$). Children in the ADVANCE group exhibited a lower incidence of emergence delirium after surgery ($p=0.038$), required significantly less analgesia in the recovery room ($p=0.016$) and were discharged from the recovery room earlier ($p=0.04$) as compared with children in the three other groups.

- A recent meta-analysis[237] that assessed the effects of non-pharmacological interventions in assisting induction of anaesthesia in children by reducing their anxiety, distress or increasing their cooperation concluded that non-pharmacological interventions, such as parental acupuncture, clown doctors, hypnotherapy, low sensory stimulation and handheld video games are promising and need to be investigated further. More specifically, six trials assessed interventions for children. Preparation with a computer package improved cooperation compared with parental presence[36]. Children playing hand-held video games before induction were significantly less anxious than controls or premedicated children[179]. Compared with controls, clown doctors reduced anxiety in children (modified Yale Preoperative Anxiety Scale (mYPAS): mean difference (MD) 30.75 95% CI 15.14 to 46.36; Vagnoli 2005[220]). In children undergoing hypnosis, there was a non-significant trend towards reduced anxiety during induction (mYPAS < 24: risk ratio (RR) 0.59 95% CI 0.33 to 1.04 - 39% versus 68%: Calipel 2005[34]) compared with midazolam. A low sensory environment improved children's cooperation at induction (RR 0.66, 95% CI 0.45 to 0.95; Kain 2001[121]) and no effect on children's anxiety was found for music therapy[104]. Parental interventions were assessed in three trials. Children of parents having acupuncture compared with parental sham-acupuncture[228] were less anxious during induction (mYPAS MD 17, 95% CI 3.49 to 30.51) and more children were co-operative (RR 0.63, 95% CI 0.4 to 0.99). Parental anxiety was also significantly reduced in this trial. In two trials[162,240], a video viewed preoperatively did not show effects on child or parental outcomes.

5.1.5 Psychological preparation/interventions for other medical procedures - what the evidence says

- Megel et al.[165] examined how parents prepared their children before preschool immunisations. Five types of preprocedural preparation/discussion were postulated: information sharing (what will happen), sensory information (how it will feel), justifying the procedure (explaining why the procedure is necessary), teaching relaxation strategies and role playing. The results suggested that parents used a mixture of various types of preparation. Seventy-five percent of children received informational preparation from their parents, typically involving a description of the events that would occur. Of the 25% of children who received no information, nine children were <3 years of age. Forty-two percent of parents also used some sensory information in their description. Forty percent of parents offered a rationale for receiving the injection. Relatively few parents (10%) offered the children any strategies for how to cope with the procedure (for example, relaxation, breathing or distraction). Unfortunately, the relationship between the type of preparation and the child's subsequent distress was not reported by the researchers.

- Uman et al.[219] assessed the efficacy of cognitive-behavioural psychological interventions for needle-related procedural pain and distress in children and young people. Only randomised controlled trials (RCTs) with at least five participants in each study group comparing a psychological intervention group with a control or comparison group were eligible for inclusion. Twenty-eight trials with 1951 participants were included. Together, these studies included 1039 participants in treatment conditions and 951 in control conditions. The most commonly studied needle-procedures were immunisations and injections. The largest effect sizes for treatment improvement over control conditions exist for distraction[37,62,186] (self-reported pain: SMD = -0.24, 95% CI = -0.45 to -0.04), hypnosis[143,144,146,147] (self-reported pain: SMD = -1.47, 95% CI = -2.67 to -0.27; self-reported distress: SMD = -2.20, 95% CI = -3.69 to -0.71; and behavioural measures of distress: SMD = -1.07, 95% CI = -1.79 to -0.35), and combined cognitive-behavioural interventions[29,40,41,143] (other-reported distress: SMD = -0.88, 95% CI = -1.65 to -0.12; and behavioural measures of distress: SMD = -0.67, 95% CI = -0.95 to -0.38). The authors commented that while there may be preliminary evidence to support the efficacy of information/preparation there is not enough evidence at this time to make strong conclusions. More specifically, Harrison[88] and Tak et al.[211] reported that information/preparation was effective in reducing observer-reported distress (SMD = -0.77, 95% CI = -0.17 to -0.38) and pulse rates (SMD = -0.47, 95% CI = -0.87 to -0.07). Although SMDs for self-reported pain and observer-reported distress both fell in the negative range (-0.22 and -0.15), their CIs passed into the positive range, indicating that while there may be preliminary evidence to support the efficacy of information/preparation on these outcomes, there is not enough evidence at this time to make strong conclusions. Information/preparation did not appear to be effective in reducing distress as assessed by behavioural measures (SMD = 0.24, 95% CI = -0.30 to 0.78), as the SMD fell in the positive range.

- Sinha et al. (2006)[206] assessed the effectiveness of distraction techniques in reducing the sensory and affective components of pain among paediatric patients undergoing laceration repair in the ED. In total, 240 children between 6 and 18 years of age were randomly assigned to an intervention or control group. Those assigned to the intervention group were given a choice of age-appropriate distracters during laceration repair. Quantitative measures of pain intensity, situational anxiety and pain distress (as perceived by the parent) were assessed by using the 7-point Facial Pain Scale, State Trait Anxiety Inventory for Children, and a visual analogue scale, respectively, before and after laceration repair. The State-Trait Anxiety Inventory for Children was performed in children $\geq$ 10 years of age. There was no difference in mean change in Facial Pain Scale scores between the control and the intervention groups in children < 10 years of age. Multivariate analysis in this same age group showed that the intervention was independently associated with a reduction in pain distress as perceived by parents based on the mean change in visual analogue scale scores. In older children, the intervention was independently associated with reduction in situational anxiety but not in pain intensity or in parental perception of pain distress.

- Haeberli et al. (2008)[86] examined whether a psychoeducational intervention might reduce the need for anaesthesia during radiotherapy (RT). A total of 223 consecutive paediatric cancer patients receiving 4141 RT fractions during 244 RT courses were studied. Whereas in 154 RT courses corresponding with 2580 RT fractions patients received no psychoeducational intervention (group A), 90 RT courses corresponding with 1561 RT fractions were accomplished by using psychoeducational intervention (group B). This tailored psychoeducational intervention in group B included a play programme and interactive support by a trained nurse according to age to get familiar with staff, equipment and the procedure of radiotherapy. Group A did not differ significantly from group B in age, gender, diagnosis, localisation of RT and positioning during RT. Whereas 33 (21.4%) patients in group A got anaesthesia, only 8 (8.9%) patients in group B needed anaesthesia. The median age of cooperating patients without anaesthesia decreased from 3.2 to 2.7 years. In both uni- and multi-variate analyses the psychoeducational intervention significantly and independently reduced the need for anaesthesia.

- Train et al. (2006)[216] evaluated the effect of a psychological approach on distress and sedation rates in children undergoing dimer captosuccinic acid-labelled with technetium-99 (99mTc) (DMSA imaging). Baseline data, on a retrospective consecutive sample of children examined using DMSA over a 6-month period (n = 81), were collected via medical note search and postal questionnaire. A further consecutive sample of 40 children was recruited prospectively to the intervention, which consisted of distraction during medical procedures and environmental manipulation. In addition half of the intervention group were provided with a photo-booklet depicting a coping child model, together with a letter offering advice to parents on how to prepare their child for the procedure. Sedation rates were lower (p=0.003) and service satisfaction ratings higher (p=0.002) in the intervention group as compared with the baseline group. Within the intervention condition, children who received the photo-booklet displayed less distress before the procedure (p=0.01) than those who did not. Also, families who received the photo-booklet were more likely to attend the appointment (p=0.024).

5.1.6 Psychological preparation for dental procedures

In dentistry, the American Academy of Pediatric Dentistry (AAPD) recognises that, in providing oral healthcare for young patients, a continuum of both non-pharmacological and pharmacological behaviour guidance techniques may be used by dental healthcare providers and recommends behavioural guidance to be used in combination with pharmacological interventions for the management of the young dental patient[15]. Techniques recommended include:

- *Tell-show-do* is a technique of behaviour shaping first described by Addelston[11] that involves verbal explanations of procedures in phrases (what, why and how a procedure will be performed) appropriate to the developmental level of the patient (tell); demonstrations for the patient of the visual, auditory, olfactory, and tactile aspects of the procedure in a carefully defined, non-threatening setting (show); and then smoothly with no break in time and without deviating from the explanation and demonstration, completion of the procedure (do). The tell-show-do technique is used with communication skills (verbal and non-verbal) and positive reinforcement[66,95].

- *Voice control* is a controlled alteration of voice volume, tone or pace to influence and direct the patient's behaviour.

- *Positive reinforcement* involves the reward of desired behaviours with social reinforcers, such as positive voice modulation, facial expression, verbal praise, and appropriate physical demonstrations of affection by all members of the dental team, and non-social reinforcers such as tokens and toys.

5.1.7 Parental desire for information

Parents are frequently dissatisfied with the lack of information they are offered and express a strong desire for perioperative information. Many healthcare professionals may withhold information because of a belief that details will induce anxiety in parents, which in turn will be communicated and increase the anxiety of children. Empirical evidence does not support this view.

- Kain et al.[120] explored parents' desire for perioperative and anaesthetic information at a pre-surgical assessment clinic visit or on the day of their children's outpatient surgery. Almost all parents (95%; n = 317) wished to receive comprehensive information concerning their child's anaesthetic, including information about all possible complications.

- Waisel and Troug[227] evaluated parents' perceived understanding and anxiety related to the discussion of the general anaesthesia risks for children that occurred during the preoperative interview with the anaesthetist, immediately prior to surgery. Approximately half the sample (N=55) was most concerned about the anaesthetic aspects of surgery (N=25), and 39% (N=21) were equally concerned about anaesthesia and surgery. Over 90% (N=50) of parents reported that the discussion of anaesthetic risks was desirable and that they understood the information. Half of the sample (N=25) felt the discussion did not change their anxiety, whereas 25% (N=13) felt it decreased anxiety and 24% (N=12) felt it increased anxiety.

- Litman et al.[148] examined parental knowledge and desire for information regarding risk of death from anaesthesia in 115 parents of healthy children undergoing elective surgery. The majority (87%) wanted to know the chance of death after anaesthesia and over half of parents (68%) had accurate knowledge of risk of death from anaesthesia. Most parents (75%) also wanted to know all possible risks, however, this was greater for mothers than fathers. A separate group of parents (N=121) were surveyed after participating in a pre-anaesthetic discussion with the anaesthetist. In 60% of cases, risk of death from anaesthesia was mentioned or implied and the proportion of parents who said they had wanted this information was similar to the previous survey. No demographic factors influenced the responses. However, several parents did not want the risk of death discussed in front of the children, who were sometimes present during the discussions.

- Franck and Spencer[70] critically analysed the published research literature (six descriptive and five intervention studies) on providing information about children's anaesthesia to parents. The intervention studies tested different methods of providing information, including verbal, video or written modalities, and showed some improvements in knowledge, anxiety and satisfaction. The authors concluded that parents want detailed information about the specifics of anaesthetic procedures, risks and personnel roles.

5.1.8 Children's desire for information

There is widespread agreement that children should be given information prior to anaesthesia, surgery and medical procedures but continuing debate about the most appropriate form and content of that information. There is little research evidence about children's concerns, fears and misconceptions about hospitals, anaesthesia and medical procedures and paucity of data regarding children's desire for perioperative information[207].

Fortier et al.[68] studied the perioperative information children want to receive from the medical staff. On the day of surgery, 143 children aged 7-17 years (ASA I or II) completed a 40-item assessment of desired surgical information and the State-Trait Anxiety Inventory for Children. Parents completed a measure assessing their child's temperament (Emotionality, Activity, Sociability and Impulsivity Survey) and the State-Trait Anxiety Inventory. The vast majority of children had a desire for comprehensive information about their surgery, including information about pain and anaesthesia, and procedural information and information about potential complications. The most highly endorsed items by children involved information about pain, including whether they would experience pain, how long it would last and how bad it would be. Children who were more anxious endorsed a stronger desire for pain information and a lesser tendency to avoid information. Younger children wanted to know what the perioperative environment would look like more than adolescent children. There were no significant correlations among child age, gender, and temperament on desire for information. Interestingly, children with a history of surgery did not require less perioperative information as compared with children who never had surgery.

5.1.9 Parental presence in anaesthesia induction

Permitting parental presence during anaesthesia induction varies widely between and within hospitals and countries[111] and is surrounded in controversy. While parental presence is routine in some hospitals and actively discouraged in others, in many cases it is based on parental advocacy balanced with the preference of individual anaesthetists carrying out the induction. Supporters of parental presence during induction of anaesthesia argue that the trauma of separation is avoided, it increases child cooperation, minimises the need for premedication, decreases the child's anxiety during induction, facilitates the long term behavioural sequelae of surgery and enhances parental satisfaction. Arguments against parental presence include the potentially unpredictable response of the parent to the situation, increased parental anxiety and distress levels, the logistics of moving parents in and out of the induction area, the extra stress on the anaesthetist due to the presence of an emotionally involved observer and potential legal ramifications of having a parent present[32,74,87,123,204,240].

The question of whether parents should stay with their child during a medical procedure has been empirically studied in many contexts apart from induction of anaesthesia, including venipuncture and immunisation, dental procedures, burn debridement, lumbar puncture, bone marrow aspirations and minor emergency procedures. In all of these contexts empirical evidence is inconclusive.

- Three studies have focused on parental presence during anaesthesia induction in relation to parents' anxiety. In a prospective study, Bevan et al.[27] examined parents of children aged 2–10 years (ASA physical status I or II) undergoing ear, nose and throat, plastic, dental, eye or urologic surgery. Of the 134 children enrolled in the study, 67 had parents present during induction (treatment group) and 67 did not (control group). Group assignment was determined by day of surgery. Parents' in-hospital anxiety was assessed in the reception and induction areas with the VAS, a 100 mm linear scale ranging from 0 to 100 ("no fear" to "great anxiety"). Parents in the treatment group had a mean VAS score of 42.8 ± 32.2 in the reception area compared to 41.9 ± 28.9 in the control group. In the induction area, the treatment group had a mean VAS score of 54.1 ± 36.4 compared to 52.3 ± 33.1 in the control group. Neither of these between-group differences were significant. Subgroups of "calm" and "anxious" parents were identified by a median split of their preoperative VAS scores. Children in the "calm treatment" "calm control" and "anxious control" subgroups were similarly upset at induction. Children in the "anxious-treatment" subgroup were the most disturbed at induction and significantly more than those in the "anxious control" subgroup. Preoperative parental anxiety levels also correlated with the child's fears (measured with the Hospital Fears Inventory[199]) and behaviours (measured with the Behavioural Questionnaire[225]) one week after surgery.

- Blesch and Fisher[28] carried out a RCT of parents of children aged 10 years or younger undergoing elective myringotomy with tube insertion, tonsillectomy and/or adenoidectomy. Of the 75 parents in the study, based on the week that their children were scheduled for surgery, 41 were assigned to be present for induction (treatment group) and 34 were not (control group). Parents' blood pressure and pulse rates were obtained as measures of anxiety at the following intervals: after consenting to the study, after separation from their children and before discharge. The state scale of the State-Trait Anxiety Inventory (STAI) was used to measure parents' subjective anxiety. After consent, the treatment group's mean blood pressure was 115/76 ± 13.7/9.8 mmHg compared to 112/72 ± 13.4/8.8 mmHg in the control group. After consent, the treatment group's mean pulse rate was 77 ± 10.2/min compared to 73 ± 10.5/min in the control group. After separation from children, the treatment group's mean blood pressure and pulse rate were 132/78 ± 19/10.9 mmHg and 81 ± 12.7/min, respectively, compared to 125/80 ± 15.4/11.5 mmHg and 75 ± 14.9/min, respectively, in the control group. Before discharge, the treatment group's mean blood pressure was 118/73 ± 12.8/11 mmHg compared to 110/71 ± 9.2/7.9 mmHg in the control group. Before discharge, the treatment group's mean pulse rate was 73 ± 7.3/min compared to 74 ± 12.6/min in the control group. The only significant differences found between the treatment and control groups were between time after consent and time after separation from their children mean diastolic blood pressures (−2.49 ± 10.63 vs. −8.24 ± 11.01, respectively; $p = 0.025$) and time after separation from their children and time before discharge mean pulse rates (7.66 ± 10.30 vs. 2.00 ± 9.07, respectively; $p = 0.016$). Subjective anxiety was not significantly different between the treatment and control group (39.05 ± 11.53 vs. 44.61 ± 14.51, respectively; $P = 0.077$).

- In a RCT Palermo et al.[177] assessed parents of infants aged 1-12 months (ASA class I and II), undergoing outpatient surgery. Of the 73 parents in the study, 37 were present during induction and 36 were not. Parental anxiety was measured with the STAI before and after surgery. There were no significant differences in anxiety between the two groups. Before surgery, parents of accompanied children had a mean STAI score of 57.6 ± 5.4 compared to 56.9 ± 6.4 for parents of unaccompanied children. After surgery, parents of accompanied children had a mean STAI score of 47.2 ± 4.8 compared to 45.2 ± 5.2 for parents of unaccompanied children. Interestingly, parents who were present during induction demonstrated comparable healthcare attitudes (measured with the Health Care Attitudes Questionnaire[85]) before and after surgery, as well as comparable levels of satisfaction with the surgical experience (measured with a modified version of the Perception of Procedures Questionnaire[127]) compared to parents who were absent during induction.

- Four studies have examined parental presence during anaesthesia induction in relation to children's anxiety. Hickmott et al.[93] undertook a RCT of children aged 1–9 years undergoing general anaesthesia for minor elective surgery. Of 49 children in the study, 26 had their mothers present during induction and 23 did not. Allocation to each group was determined by the week in which the children's surgery took place. A recovery room or ward nurse, not involved in the anaesthetic procedure, was responsible for observing and measuring children's anxiety levels in the anaesthesia room. Time in the anaesthesia room was separated into the 'waiting period' (time from the children's arrival until the anaesthetist arrived) and the 'induction period' (time from the anaesthetist's arrival). Children's anxiety was measured using a pre-determined scale ranging from 0 (no anxiety) to 2 (marked anxiety) during the waiting period and 0 (calm) to 4 (screaming and uncontrollable) during the induction period. During the waiting period in the mother-present group, five children scored 0 and two children scored 2; whereas, in the mother-absent group, seven children scored 0 and one each scored 1 and 2. During the induction period in the mother-present group, 13 children scored 0, nine scored 1, and two each scored 2 and 3; whereas, in the mother-absent group, 15 children scored 0, four scored 1, three scored 2, and one scored 3. Children's anxiety levels did not differ significantly between the two groups during either the waiting or the induction period (Mann–Whitney U test).

- In a RCT, Amanor-Boadu[14] assessed 118 children aged 1–12 years undergoing inguinal surgery as day cases. Children undergoing surgery were randomly assigned to be accompanied or unaccompanied. Of the 118 children in the study, 52 were accompanied by a parent and 66 were not. Children were evaluated according to their age group, that is, aged 5 years or less and more than 5 years. Heart rates using a stethoscope were taken both on the ward and before induction as a measure of anxiety. For children 5 years or less, unaccompanied children had a mean heart rate of 109 ± 13/min on the ward compared to 111 ± 12/min for accompanied children. For children more than 5 years, unaccompanied children had a mean heart rate of 101 ± 11/min on the ward compared to 100 ± 10/min for accompanied children. These two differences were not significant. Mean heart rates before induction, for children 5 years or less, was 128 ± 20/min for unaccompanied children compared to 118 ± 16/min for accompanied children. For children more than 5 years, it was 108 ± 10/min for unaccompanied children compared to 97 ± 19/min for accompanied children. Both of these differences were significant at $p = 0.001$.

- In a retrospective study using a multiple matched concurrent cohort, Kain et al.[106] examined children's anxiety in relation to parents'. The participants were selected from a database of children from a number of previous prospective and randomized studies that the authors conducted comparing parental presence with no parental presence. Of the 568 children included in the study (aged 2–12 years undergoing general anaesthesia for elective outpatient surgery), 284 had their parent present during induction and 284 did not. For children, anxiety was measured with the modified Yale Preoperative Anxiety Scale (mYPAS) and children were categorized as "anxious" if they scored >40 on the mYPAS, and as "calm" if they scored <30 on the mYPAS. For parents, anxiety was measured with the STAI and parents were categorized as "anxious" if they scored in the upper 50% on the STAI, and as "calm" if they scored in the lower 50% on the STAI. Four groups of child-parent pairs were then retrospectively compared for the parent-present and parent-absent groups: calm parent-calm child, anxious parent-calm child, calm parent-anxious child and anxious parent-anxious child. Anxious children with calm parents present were significantly less anxious during induction than anxious children with no calm parents present (mean mYPAS = 51.9 ± 24 vs. 64.6 ± 26, respectively; P = 0.03). Calm children with anxious parents present were significantly more anxious during induction than calm children with no anxious parents present (mean mYPAS = 52.4 ± 28 vs. 39.4 ± 21, respectively; p = 0.002). On the other hand, there was no significant difference in anxiety during induction between calm children with calm parents present and calm children with no calm parents present (mean mYPAS = 39.9 ± 22 vs. 34.7 ± 20, respectively; p = 0.15), and no significant difference in anxiety during induction between anxious children with anxious parents present and anxious children with no anxious parents present (mean mYPAS = 71.0 ± 23 vs. 66.6 ± 27, respectively; p = 0.49). The authors concluded that the presence of a calm parent does benefit an anxious child during induction of anaesthesia and the presence of an overly anxious parent has no benefit.

- In a RCT, Patel et al.[179] examined 112 children aged 4–12 years undergoing outpatient surgery. Children's change in anxiety was assessed from baseline to introduction of the anaesthesia mask using the mYPAS. Children were randomly assigned to one of three groups using sealed envelopes: parental presence (n = 36), parental presence plus 0.5 mg/kg oral midazolam (n = 38), or parental presence plus a hand-held video game (n = 38). Children who received parental presence plus a hand-held video game experienced a statistically significant decrease in anxiety from baseline to introduction of the anaesthesia mask compared to children who received parental presence alone (median change in mYPAS = −3.3 vs. +11.8, respectively; p = 0.04). Children who received parental presence plus midazolam did not experience a statistically significant change in anxiety from baseline to introduction of the anaesthesia mask compared to the other two groups (median change in mYPAS = +7.3).

- Seven studies examined both parents' and children's anxiety in relation to parental presence during anaesthesia induction. Johnston et al.[102] carried out a prospective study of parents and their children aged 2–8 years undergoing day surgery. Of the 134 children in the study, 67 had their parent present and 67 did not. Parents and children were assigned to each group based on the day of the week that surgery was scheduled. Anxiety was measured before induction. For parents, the VAS, a 10 cm line ranging from 0 ("no anxiety") to 10 ("most anxiety"), was used to measure anxiety. For children, the Global Mood Scale (GMS), an observation scale ranging from 1 (child attentive and happily active) to 7 (child screaming), was used. Overall, there were no differences in parents' or children's anxiety between parent-present and parent-absent groups. To conduct further analysis, the authors separated parents into low-anxiety and high-anxiety groups based on their VAS scores; that is, those who scored ≤3 on the VAS were considered low-anxiety, and those who scored ≥6 on the VAS were considered high-anxiety. The authors found that high-anxiety parents who were present for induction were more anxious than high-anxiety parents who were not present for induction. Low-anxiety parents who were present for induction were less anxious than low-anxiety parents who were not present for induction. Children with high-anxiety parents who were present were more anxious than children with high-anxiety parents who were not present. Children with low-anxiety parents experienced the same level of anxiety whether they were in the parent-present or parent-absent group.

- In a non-randomised prospective study Cameron et al.[35] assessed 74 parents and their children aged 1–8 years undergoing day surgery. Parents were only allowed to be present for induction if the anaesthetist carrying out the induction granted them permission. The treatment group consisted of 38 parents who were granted permission and decided to be present. The control group consisted of 36 parents who were either not permitted or decided not to be present. In the control group, 22 parents chose to separate from their children in the theatre holding bay area and 14 parents chose to separate from their children in the day surgery ward. Parents' anxiety was measured immediately upon separation from their children using a VAS with scores ranging from 1 ("no anxiety at all") to 10 ("most anxiety anyone could have"). A five-point scale with scores ranging from 1 (cheerful and attentive) to 5 (very distressed and uncontrollable) was used by parents to assess their children's anxiety right before separation from them. Parents in the treatment group were significantly less anxious, as measured by the VAS, than parents in the control group (mean = 3.4 ± 1.6 vs. 6.5 ± 2.2, respectively; $p < 0.001$). Parents who were present for induction reported their children to be significantly less anxious than parents who were not present for induction (mean = 1.9 ± 1.1 vs. 2.8 ± 1.1, respectively; $p < 0.001$).

- In a RCT, Kain et al.[116] examined parents and their children aged 1–6 years undergoing general anaesthesia for elective outpatient surgery. Of the 84 children in the study, using a random numbers table generated by a computer, 43 were randomised to have their parent present during induction (intervention group) and 41 did not (control group). For children, anxiety was measured with the Yale Preoperative Anxiety Scale (YPAS), Clinical Anxiety Rating Scale (CARS), VAS and cortisol. For parents, anxiety was measured with the STAI, VAS, heart rates and blood pressure. The VAS, a 100-mm line ranging from 0 ("not anxious") to 100 ("extremely anxious"), was used as an observational measure for children and a self-report measure for parents. Using these measures, no significant differences were found between the two groups for either children's or parents' anxiety. For children, anxiety was reported as medians and 25–75% interquartile ranges for the holding area, induction 1 (entering the induction room) and/or induction 2 (introduction of anaesthesia mask). On the VAS, children in the control group compared to those in the intervention group scored the following: holding area = 11 (0–28) vs. 6 (0–33), respectively; induction 1 = 38 (0–89) vs. 37 (0–82), respectively; and induction 2 = 43 (5–78) vs. 45 (8–86), respectively. On the YPAS, children in the control group compared to those in the intervention group scored the following: induction 1 = 34 (24–41) vs. 30 (25–41), respectively, and induction 2 = 38 (24–65) vs. 42 (30–62), respectively. On the CARS, children in the control group compared to those in the intervention group scored the following: induction 1 = 0 (0–1) vs. 0 (0–1), respectively, and induction 2 = 1 (0–4) vs. 1 (0–4), respectively. With respect to cortisol (µg/ml) for induction 2, the results for children in the control group compared to those in the intervention group were 73 (51–100) vs. 76 (48–91), respectively. For parents, anxiety was reported as means and standard deviations or as medians and 25–75% interquartile ranges for the holding area and/or post-induction (after parents left their children). State-Trait Anxiety Inventory scores for the control and intervention group parents were 46 ± 12 vs. 43 ± 12, respectively, post-induction. VAS scores for the control group parents compared to the intervention group parents were 43 (20–58) vs. 38 (13–49), respectively, in the holding area and 49 (18–73) vs. 41 (5–66), respectively, post-induction. Systolic blood pressure (mmHg) for the control group parents compared to the intervention group parents was 114 ± 11 vs. 116 ± 17, respectively, in the holding area and 122 ± 12 vs. 121 ± 13, respectively, post-induction. Diastolic blood pressure (mmHg) for the control group parents compared to the intervention group parents was 71 ± 8 vs. 67 ± 10, respectively, in the holding area and 77 ± 9 vs. 75 ± 7, respectively, post-induction. Heart rates (beats/minute) for the control group parents compared to the intervention group parents were 81 ± 9 vs. 78 ± 8, respectively, in the holding area and 85 ± 10 vs. 84 ± 8, respectively, post-induction. The authors concluded that only children who were older than 4 years, had a parent with a low trait anxiety level or a low baseline level of activity as assessed by temperament ratings benefited from parental presence during induction of anaesthesia. In contrast, there was a trend among children younger than 4 years to be more anxious during induction in the presence of their parent.

- Kain et al.[118] in a RCT studied 88 parents and their children aged 2–8 years undergoing general anaesthesia for elective outpatient surgery. The children were randomized into one of three groups according to a random numbers table: (a) parental presence (n = 29); (b) premedication with 0.5 mg/kg oral midazolam mixed in 10 mg/kg acetaminophine syrup at least 20 minutes before surgery (n = 33); (c) no parental presence and no sedative premedication (n = 26). Anxiety was measured for parents with the STAI and for children with the Procedural Behavior Rating Scale (PBRS[126]). There were no significant differences between the three groups regarding children's anxiety in the preoperative holding area. Upon separation from their parents, children in the midazolam group were significantly less anxious than children in the other two groups (PBRS = 0 (0–1) vs. 4 (0–5); p = 0.02). Children in the midazolam group were also significantly less anxious than children in the other two groups at both entrance to the operating room (p = 0.0171) and introduction of the anaesthesia mask (p = 0.0176). Parents in the midazolam group were significantly less anxious after separation than parents in the parental presence group and parents in the control group (mean STAI score = 43 ± 12 vs. 50 ± 10 vs. 47 ± 10, respectively; p = 0.048). The percentage of inductions in which compliance of the child was poor was significantly greater in the control group compared with the parental presence and midazolam groups (25% vs. 17% vs 0%; p= 0.013)

- Kain et al.[119] in a RCT assessed 103 parents and their children aged 2–8 years. Parents and their children were randomly assigned to each group using a random numbers table. The intervention group had parental presence and received premedication with oral midazolam syrup (0.5 mg/kg at least 20 minutes before surgery. The control group received premedication with oral midazolam syrup (0.5 mg/kg) at least 20 minutes before surgery only. Anxiety was measured for children with the mYPAS and for parents with the STAI. Children's anxiety was not significantly different between the two study groups (p = 0.49). Parents' anxiety, on the other hand, was significantly lower after separation for those who were present compared to those who were not present (mean = 43 ± 11 vs. 48 ± 12, respectively; p = 0.037). Parental satisfaction with the overall care provided and with the separation process was significantly higher among the premedication and parental presence group compared with the premedication only group.

- Kain et al.[107] undertook a RCT of parents and their children undergoing general anaesthesia and elective outpatient surgery. Of the 80 children in the study, 29 had their parent present, 27 had their parent present and received oral midazolam (0.5 mg/ kg) about 30 minutes before induction, and 24 did not have their parent present (control group). They were randomly assigned to the three groups based on a random number table. For children, anxiety was measured with the mYPAS and for parents with the STAI. Heart rates, skin conductance levels (SCL) and blood pressure levels were also used to measure parents' anxiety. Children in the parental presence plus midazolam group were less anxious than children in either the control group or the parental presence only group ($p = 0.023$). At different time points, parents in both parental presence groups had higher anxiety, as measured by heart rates, than the control group ($p < 0.05$). However, there was no significant difference in heart rates between the parental presence and parental presence plus midazolam groups. Skin conductance level was higher in the two parental presence groups than in the control group ($p < 0.05$). However, there was no significant difference in SCL between the two parental presence groups. The SCLs were not provided by the authors. There were no significant differences between the parental presence, parental presence plus midazolam and control groups with regards to systolic blood pressure (123 ± 21 vs. 128 ± 16 vs. 126 ± 19, respectively; $p = 0.59$) and diastolic blood pressure (82 ± 14 vs. 85 ± 13 vs. 81 ± 15, respectively; $p = 0.88$) after induction. In addition, there were no significant differences in parents' self-reported anxiety, as measured by the STAI, between the three groups (STAI scores and p values were not provided).

- Kain et al.[109] undertook a prospective study of parents and their children (mean age = 4.9 years) who were part of a previous investigation by the authors at their initial surgery and were undergoing a subsequent surgery. At their initial surgery, the children had been assigned to the following preoperative intervention: parental presence ($n = 27$), oral midazolam ($n = 13$), parental presence plus oral midazolam ($n = 10$) and no intervention ($n = 33$). The authors allowed parents to choose their preoperative intervention group at the subsequent surgery. The parents of the 83 children in the study chose the following preoperative intervention: parental presence ($n = 46$), oral midazolam ($n = 8$), parental presence plus oral midazolam ($n = 21$) and no intervention ($n = 8$). Anxiety was measured for children with the mYPAS and for parents with the STAI. There were no significant differences between the groups regarding children's anxiety upon entering the operating room (median mYPAS score [range]: parental presence = 45.8 [22.9–91.7], oral midazolam = 54.2 [22.9–95.8], parental presence plus oral midazolam = 35.4 [22.9–100.0], and no intervention = 23.2 [22.9–45.8; $p = 0.31$) or during induction (median mYPAS score [range]: parental presence = 45.8 [22.9–100.0], oral midazolam = 65.5 [22.9–95.8], parental presence plus oral midazolam = 34.2 [22.9–100.0], and no intervention = 24.5 [22.9–50.0]; $p = 0.15$). There was also no significant difference in parents' anxiety at separation (mean STAI score: parental presence = 42.8 ± 11.1, oral midazolam = 49 ± 6.5, parental presence plus oral midazolam = 43.3 ± 13.0 and no intervention = 37.8 ± 6.5; $p = 0.28$). Children in the midazolam group experienced significantly higher anxiety in the preoperative holding area than children in the other groups (median mYPAS score [range]: parental presence = 23.3 [23.3–70.0], oral midazolam = 37.5 [23.3–68.8], parental presence plus oral midazolam = 45.8 [23.3–96.7], and no intervention = 23.3 [23.3–55.0]; $p = 0.03$). Parents of children in the midazolam group were also significantly more anxious than parents of children in the other groups in the preoperative holding area (mean STAI score: parental presence = 38.6 ± 9.1, oral midazolam = 47.3 ± 8.4, parental presence plus oral midazolam = 42.5 ± 12.2 and no intervention = 36.8 ± 5.1; p = 0.09). Interestingly, of parents whose children received parental presence at the initial surgery, 70% chose to be present during induction again. In contrast, only 23% of the patients who received midazolam at the initial surgery requested midazolam at the subsequent surgery and only 15% of the patients who received no intervention at the initial surgery requested no intervention at the subsequent surgery. Parents' intervention preferences at the subsequent surgery were influenced by children's anxiety at the initial surgery.

- Arai et al.[18], in 22 pairs of mothers and children (1-3 years old) scheduled for minor plastic surgery under general anaesthesia found that higher parental anxiety pre-surgery, as indicated by higher amounts of maternal salivary amylase activity, was significantly correlated with higher children's anxiety during induction (r_s = -0.667, p < 0.0001) and severer children's emergence agitation (r_s= 0.705, p < 0.0001). Both children's anxiety and agitation were rated by a blind observer.

- In another study[17] the same authors randomised, using computer-generated random numbers, 58 children, aged 1-3 years, classified as ASA I, undergoing minor plastic surgery under general anaesthesia to one of three groups: (a) a sedative group (0.5 mg/kg oral midazolam) (n= 19); (b) parental presence (20); (c) a sedative and parental presence (19). Children in the midazolam group showed a better quality of mask induction compared with those on the parental presence group but the addition of parental presence to oral midazolam did not provide additional improvement of mask induction. In contrast, the children in the midazolam and parental presence group were less agitated than those in the other groups at emergence from anaesthesia.

- A recent meta-analysis[237] that assessed the effects of non-pharmacological interventions in assisting induction of anaesthesia in children by reducing their anxiety, distress or increasing their cooperation concluded that the presence of parents during induction of general anaesthesia does not reduce their child's anxiety. However, the authors commented further that calm parents may be helpful and parental presence should be considered on an individual basis.

Taken in combination the results of the above randomised studies indicate that current evidence shows that there is no apparent benefit of parental presence during anaesthesia induction in relation to decreasing parents' and children's anxiety[39]. In many cases, midazolam or distraction techniques appear to be a suitable substitute. Overall, positive effects for parental presence, including lower levels of child anxiety and distress, have been reported in studies in which parents were not randomly assigned to condition but were permitted to self-select presence or absence. In terms of child characteristics, a prospective cohort study has demonstrated that children who benefit from parental presence are older, have lower levels of activity in their temperament and have parents who are calmer and who value preparation and coping skills for medical situations[114].

5.1.10 Parental presence during medical procedures

Piira et al.[183] conducted a systematic review, of controlled studies investigating parental presence in the paediatric treatment room at the time of their child's medical procedure. A total of 28 studies met the inclusion criteria, which were as follows: the studies evaluated the effects of parental presence on child, parent or health professional outcomes; concurrent control groups were used; only primary data were used to avoid bias resulting from the use of duplicate results. The age of the children participating in the studies ranged from 2 weeks to 18 years. 1256 children had a parent present and 1025 children did not have a parent present. The medical experiences included routine immunisations, venipunctures, dental procedures, lumbar punctures, burns treatments, intubation, central line placement, chest tube placement and anaesthesia induction, with some studies including a number of different painful contexts. There were mixed findings regarding the effect of parental presence on measures of child distress and affect; however, studies of lower levels of evidence were more likely to report significant results. Parents who were present during their child's medical intervention were either better off or no different from parents who were absent with regard to their levels of distress and satisfaction. There was no evidence of increased technical complications nor elevated staff anxiety for health professionals attending to children with a parent present as compared to attending to children without their parents.

5.1.11 The role of the parents during medical procedures and/or anaesthesia induction

In the paediatric pain literature a number of studies point to the role that parents play in shaping their child's pain perception and distress response. Certain parental behaviours are associated with child coping and others with child distress when children undergo painful medical procedures. Parenting behaviours such as agitation, provision of reassurance, empathic comments, giving control, excessive explanations and apologies to their children have been shown to be associated with (and indeed precede) elevated distress and increased pain intensity during medical procedures[30,31,48]. Humour, commands to use coping strategies and non-procedural talk are associated with increases in child's coping. Dahlquist and colleagues[47] demonstrated the influence of speech function on pain distress. Their results showed that vague commands by caregivers were positively associated with child distress during painful procedures. Liossi and colleagues[145] showed that parental expectancies are highly predictive of experienced pain in children undergoing lumbar punctures.

Parents are often anxious not only about their child's distress but also about their own ability to support and comfort their child through a painful experience. Thus, parents need to be included in interventions and helped to control their own anxiety, which in turn will ensure less anxiety being communicated to the child. Simple educational leaflets can give useful information and more extensive training programmes can teach parents what to do[185].

5.1.12 Summary - preparation for sedation

In summary, current evidence from the literature dealing with patient preparation, that is, preparation for anaesthesia and medical procedures suggests:

- that preparation for sedation is important for young people and their parents
- there is some helpful direction informing what this should and should not include and how it is performed.

For children, the extensiveness and style of preparation should be guided by each child's age and developmental level

In general, specific discussion about the sedation and procedure has more relevance for children >2 years of age. The outcome from this narrative review suggests that preparation should have at least three components, namely:

- what will happen (where, how long it will last and what will be done)
- how it will feel (pressure, temperature and level of discomfort to be expected)
- strategies to cope with the stressor (which may be related to the sedation technique and/or procedure[57,182,210].

Given this, children can be asked what strategies they think will help them to cope and, if possible, those strategies should be incorporated into the sedation administration. In addition, given the strong data supporting distraction, distraction techniques should be used during the induction of sedation. Evidence supporting the use of behavioural strategies, such as teaching children coping techniques to alleviate their preoperative anxiety, has emerged throughout the literature[236]. Teaching children coping skills allows them to learn how to calm themselves in times of stress and thus may be useful not just at the time of the procedure in question but at subsequent procedures as well.

For parents, there is inconclusive evidence indicating whether parents should be encouraged or discouraged to be present at their child’s induction. The offer to be present is therefore based on negotiation with the care team. Although parental presence may not have a clear, direct influence on child distress and behavioural outcomes, there are potential advantages for parents and children; offering the option of parental presence is clearly in line with a paradigm shift to family-centred care during hospitalisation[112]. Parental inclusion in supporting interventions may also help their own anxiety, lessening the potential for this to be communicated to their child.

6 Drugs for sedation in infants, children and young people

6.1 General clinical introduction: drugs for sedation in infants, children and young people

The Guideline Development Group (GDG) considered that many potentially useful sedation drugs could be reviewed. The GDG decided to limit the literature searches and discussions to sedative drugs that were both currently available and in common use in the UK. All commonly used routes of administration of the chosen drugs, for example by injection, by mouth or by inhalation, were considered.

The GDG was mindful of the fact that some classes of sedative drugs may be used for analgesia, pre-operative or pre-induction medication and in some situations, may cause general anaesthesia. Evidence for sedation was considered only if the studies reviewed specifically intended to assess the sedative effects of the drug. The GDG made a judgment on whether the doses used were likely to cause anaesthesia.

The GDG reviewed evidence on the following drugs:

- Midazolam: Oral, IV, rectal, transmucosal
- Ketamine: IV, IM
- Chloral Hydrate: Oral
- Triclofos sodium: Oral
- Nitrous oxide: Inhalation
- Sevoflurane: Inhalation
- Propofol: IV
- Opioids: IV Fentanyl, IV Morphine and intranasal (IN) Diamorphine

Midazolam is a short acting benzodiazepine with a short half life. It has anxiolytic, amnestic, hypnotic and anticonvulsant properties. It can be administered by several different routes and is often given in combination with other sedative agents.

Ketamine is an N-methyl d-aspartate (NMDA) receptor antagonist which causes a trance-like sedation with few appreciable effects on the respiratory and cardiovascular systems. Its analgesic effect is a major advantage. Administered intravenously it can be titrated. A single intramuscular dose is predictable and effective whenever venous access is impractical.

Chloral hydrate was the first synthetic drug employed for its sedative-hypnotic effect. Unlike opioids, it produces sedation without significant adverse effects on cardiovascular or respiratory function at therapeutic doses. In children it is orally administered for painless imaging.

Nitrous oxide gas, delivered with oxygen, also acts as an NMDA receptor antagonist. It has a rapid anxiolytic/sedative/analgesic effect and is delivered by inhalation. Doses may be titrated to achieve target effect.

Opioid drugs can be used as sedatives for painful procedures however it is important to separate the use of opioids used as sedation from when they are used specifically for analgesia alone. Intravenous morphine and fentanyl are commonly used opioids whose sedative action can be improved by the addition of another drug such as midazolam. Intranasal diamorphine has been considered in the review because it has the potential to be rapidly effective and easily administered.

Propofol is a short acting hypnotic agent that can be given in low doses to achieve short acting and controlled sedation. Propofol is not considered an analgesic, so opioids such as fentanyl may be combined with propofol to alleviate pain. Propofol is administered intravenously.

Sevoflurane is a fluorinated isopropyl ether which has a rapid induction and quick elimination effect. It is delivered by inhalation and may be titrated for sedative effect.

Triclofos is a sedative-hypnotic drug, similar to chloral hydrate but with less gastric irritation. It is orally administered for painless imaging.

The GDG reviewed evidence on sedative drugs with the following comparisons:

- Placebo; non-pharmacological treatment
- Head to head
- Combination (including analgesia and general anaesthesia)
- Route of administration
- Dose

In some settings, the use of local anaesthesia was included because the effect of analgesia is likely to be crucial to the success of any sedation for painful procedures.

In general, for the purposes of categorisation of RCTs, a drug combination is defined as two or more drugs that have sedative potential. In some RCTs, single sedation drugs have been combined with interventions that do not cause sedation such as local anaesthesia, mild analgesics (such as paracetamol) or a non-pharmacological intervention. For the purposes of categorisation of the RCTs, these additional interventions are not considered to be part of a sedation drug combination when they have been applied equally to both groups. For example in a RCT in which one group receives sedation drug A and the other has sedation drug B, but both groups receive local anaesthesia, the RCT is categorised as a single drug comparison. However if local anaesthesia had been used only in one group the RCT would be categorised as a comparison of a drug combination.

After reviewing and assessing the evidence for each drug, this chapter evaluates the specific clinical settings in which they are used (Section 6.12). The GDG sought to group the evidence and the recommendations according to the following type of procedure:

- painless imaging
- painful procedures
- dental procedures
- endoscopy

The GDG believe this classification covers the majority (more than 90%) of common procedures.

6.2 General methodological introduction: drugs for sedation in infants, children and young people

Efficacy outcome data for this review was taken from RCTs alone. Each outcome was quality assessed using a GRADE evidence profile. The outcome measures for drug efficacy that were considered by the GDG were as follows:

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 for example Visual Analogue Scale (VAS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), Faces Pain Scale (FPS)
    - 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
    - recovery: time from completion of procedure to recovery criteria being met or recovery to pre-sedation state
    - duration of procedure
    - total: time from administration of intervention to when patient has been transferred to the recovery area or has been discharged

Evidence of safety was sought from both RCTs and non RCT observational studies. The outcomes of interest in each RCT were evaluated using a GRADE evidence profile. The GDG recognised that research from non RCT observational studies is subject to the usual limitations of observational work, including dependence on the quality of medical record documentation and potential for bias secondary to non randomisation, and un-blinded participants. In these studies, there were no interventions or comparisons but merely data collection of adverse events. The datasets were generally large, and were expected to provide more information on a range of adverse events than the small RCTs available for review. Due to these limitations, we only assigned quality rating ('very low' quality) based on the GRADE scheme. It was considered more comprehensive to present separately this supplementary observational data in the form of concise, customised summary tables which also contain the GRADE ratings.

The outcomes measures for safety were limited to short term effects. Long term effects of sedation drugs were considered to be too rare for inclusion in this review. The outcome measures for drug safety and adverse effects that were considered by the GDG are as follows:

- Aspiration
- Respiratory intervention, including:
    - oral-pharyngeal airway
    - endotracheal intubation
    - assisted ventilation
- Cardiac arrest requiring either/or:
    - external cardiac massage
    - defibrillation
- Oxygen desaturation <90%
- Vomiting

A decrease in oxygen saturation to below 90% was chosen as a safety outcome. Oxygen saturation often fluctuates during recovery from anaesthesia, especially if supplemental oxygen is not administered; The GDG agreed however that desaturation less than 90% is concerning.

The GDG agreed that the dose of drugs was an important consideration. Matching the dose to the target sedation level is essential and when robust data has been published, it has been quoted. Yet the dose *question* is not straightforward. When a drug is given by mouth, only a single dose is practical because its absorption, and therefore its maximum effect, can take a variable time. In contrast, intravenous drugs can be titrated to achieve the target level of sedation although it must be appreciated that there is considerable variation and the practitioner will need to continually assess the conscious level and adjust the dose accordingly. Prolonged recovery is a hazard that can be avoided if the lengths of action of the sedation drugs match the length of the procedure. This is a notoriously dangerous problem following painful procedures when pain has subsided, for example after a dental extraction, because the sedation is no longer opposed by the stimulation of painful procedure.

6.3 Midazolam

Matrix of midazolam comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Morphine = Mo
Meperidine = Me
Isoflurane = I
Ketamine=K
Local anaesthesia = LA
Topical anaesthesia = TA
Midazolam = M
Nitrous oxide = N_20
Nitrous oxide and oxygen = N_20+02
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Midazolam vs.

	Reference	Tables	Evidence statements page
Placebo			
	Liacouras, 1998[140] Mortazavi, 2009[170]	Table 2	172
	Fatovich 1995[63], Luhman 2001[152]	Table 3	176 173
	Kapur 2004[125]	Table 4	173
	Fishbein 1997[67]	Table 5	176
	Ljungman 2000[149] Theroux 1993[212]	Table 6	173 174
Head to head			
M vs TS	Singh 2002[205]	Table 7	174
M vs CH	Layangool 2008[136]	Table 8	174
M + non-pharma vs N_20 + pharma	Zier 2008[239]	Table 9	175
Combinations			
M vs M + N_20+02	Al-zahrani 2009[13]	Table 10	175
M + N20 vs N20	Luhman 2001[152]	Table 11	176

M + P vs P	Paspatis 2006[178] Disma 2005[56]	Table 12 Table 13	176 176
M + Morphine vs Propofol + Morphine	Havel 1999[91]	Table 15	177
M + Meperidine vs Meperidine	Fishbein 1997[67]	Table 14	176
M + F vs F	Antmen 2005[16]	Table 16	177
M + Remifentanil vs Remifentanil	Antmen 2005[16]	Table 17	178
M + K vs K + placebo	Sherwin 2000[203] Wathen 2000[229] Dilli 2008[55]	Table 18	178
Safety			
RCTs	Liacouras 1998[140] Luhmann 2001[152] Ljungman 2000[149] Layangool 2008[136] Zier 2008[239] Disma 2005[56] Havel 1999[91] Antmen 2005[16] Wathen 2000[229] Sherwin 2000[203] Dilli 2009[54]	Table 19 Table 24	
Aspiration	Luhmann 2001[152] Havel 1999[91] Wathen 2000[229] Sherwin 2000[203]		181
Desaturation	Liacouras 1998[140] Disma 2005[56] Havel 1999[91] Antmen 2005[16] Wathen 2000[229] Sherwin 2000[203] Hartgraves 1994[90] Needleman 1995[173]	Table 26 Table 27	181
Respiratory intervention	Luhmann 2001[152] Disma 2005[56] Havel 1999[91] Wathen 2000[229] Sherwin 2000[203] Needleman 1995[173] Kanegaye 2003[124]	Table 26 Table 27	181
Vomiting	Luhmann 2001[152] Ljungman 2000[149] Layangool 2008[136]	Table 26 Table 27	181

	Zier 2008[239] Antmen 2005[16] Wathen 2000[229] Sherwin 2000[203] Everitt 2002[60] Shashikiran 2006[202] Fuks 1994[71] Needleman 1995[173] Kanegaye 2003[124]		
Observational	Peña 1999[180] Hulland 2002[98] Pitetti 2003[184] Roback 2005[191] Mamula 2007[157] Sacchetti 2007[197] Lightdale 2009[141]	Table 26 Table 27	181
Route of administration			
Oral / intranasal	Connors 1994[42] Everitt 2002[60] Hartgraves 1994[90] Lightdale 2009[141]	Table 20 Table 21	179
Intranasal / IM	Shashikiran 2006[202]	Table 22	180
Dose			
	Fuks 1994[71] Fukuta 1994[72] Kanegaye 2003[124]	Table 23 Table 25	181

6.3.1 Clinical methodological introduction for midazolam

CLINICAL QUESTIONS

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?

- safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy of midazolam. The search was expanded to include non-RCT observational studies for the safety of midazolam.

There were no systematic reviews identified for the use of midazolam in paediatric sedation.

Twenty seven RCTs comparing midazolam in any route with other sedative drugs were assessed for efficacy and safety.

Seven non-RCTs observational studies in 5,412 patients assessed the safety of midazolam.

Crossover trials were treated separately from parallel armed trials unless there was sufficient data to allow their combination.

Meta-analyses for RCTs were performed where drug interventions and comparisons and outcomes were sufficiently homogenous and studies were combined regardless of dose, duration of intervention, procedure (within painful and non-painful groups), setting (e.g. dentistry, accidents and emergencies) and age.

6.3.2 Evidence profiles for midazolam

6.3.2.1 RCT evidence profiles for efficacy and safety for midazolam

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

PLACEBO COMPARISONS OR NON-DRUG TREATMENT

Table 2: Oral midazolam vs. placebo/no drug treatment; Liacouras 1998[140], Mortazavi 2009[170]

Question: Should oral midazolam vs. placebo be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology and outpatients (dental postgraduate paediatric clinic)
Bibliography: Liacouras 1998[140] (intravenous placement); Mortazavi 2009[170] (dental extractions, teeth restorations, pulpotomies)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam[6]	placebo	Relative (95% CI)	Absolute		
Completion of procedure (Mortazavi 2009[170])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/20 (45%)	20/20 (100%)	RR 2.16 (1.34 to 3.47)[2]	0 more per 1,000	LOW	
Completion of procedure (Liacouras 1998[140])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/62 (95.2%)	47/61 (77%)	RR 1.24 (1.07 to 1.43)[4]	185 more per 1000 (from 54 more to 331 more) 0 more per 1,000	MODERATE	
Adverse events: Oxygen desaturation <90% (Mortazavi 2009[170])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	0/20 (0%)[2,5]	0/20 (0%)	not pooled	-	LOW	

[1] Mortazavi 2009[170]: double blind study however partial allocation concealment and unclear blinding of outcome assessor and unclear ITT and N=20 (small study)
[2] p=0.002
[3] Liacouras 1998[140]: unclear if ITT analysis was done; also large loss to follow up (>20%) for the outcome of patients satisfaction: for 32/123 (26%) patients, data was not available and this was greater in the control group (18/61=30%) compared to the intervention group (14/62=23%)
[4] p=0.005
[5] Mortazavi 2009[170]: study stated that all patients remained close to 100% oxygen desaturation during procedure
[6] For two RCTs, there was highly significant heterogeneity (I2=83%; p=0.02). Thus, the studies are presented individually.
Note: The Mortazavi study[170] used the Houpt scale to evaluate overall behaviour. One of the six ratings within this scale is called ‘aborted’, defined as ‘no treatment rendered’, so we used those data to calculate the number of patients who completed the procedure in each group.

Table 3: Oral midazolam vs. placebo; Fatovich 1995[63], Luhman 2001[152]

Question: Should oral midazolam vs. placebo (with local anaesthesia in both groups) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: A & E
Bibliography: Luhman 2001[152] (suturing for laceration repair) Fatovich 1995[63] a) (suturing for laceration repair) Fatovich 1995[63] b) (suturing for laceration repair)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam	placebo	Relative (95% CI)	Absolute		
Completion of procedure (Luhman 2001[152])												
1	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/52 (98.1%)	50/50 (100%)[1]	RR 0.98 (0.93 to 1.04)	20 fewer per 1000 (from 70 fewer to 40 more)	MODERATE	
Anxiety – child assessed by observers using a validated scale (Herbertt-Michaelinees-Venham scale) (Fatovich 1995[63])												
1	randomised trial	no serious limitations[2]	no serious inconsistency	no serious indirectness	serious[3]	none	33/57 (57.9%)	32/50 (64%)[4]	RR 0.89 (0.66 to 1.21)	70 fewer per 1000 (from 218 fewer to 134 more)	MODERATE	
Distress – child assessed by parents using a validated scale (measured with: Visual Analogue Scale (VAS); Better indicated by less) (Fatovich 1995[63])												
1	randomised trial	no serious limitations[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57	50	-	MD -1.6 (-2.81 to -0.39)[5]	MODERATE	
Adverse events: Aspiration (Luhman 2001[152])												
1	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/51 (0%)[7]	0/50 (0%)	not pooled	-	MODERATE	
Adverse events: Respiratory intervention (Luhman 2001[152])												
1	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	0/51 (0%)[8]	0/50 (0%)	not pooled	-	MODERATE	
Adverse events: Vomiting (Luhman 2001[152])												
1	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[9]	none	0/51 (0%)[9]	0/52 (0%)	not pooled	-	MODERATE	

[1] Luhman 2001[152]: p=0.49
[2] Fatovich 1995[63]: unclear ITT and unclear drop out rate; otherwise adequate allocation concealment and double blind
[3] wide confidence intervals
[4] Fatovich 1995[63]: p=0.47
[5] Fatovich 1995[63]: p=0.009

[6] Luhman 2001[152]: adequate concealment and low loss of follow up (1 patient in the midazolam group); however single blind study (only assessors were blind) and ITT was not performed - per protocol analysis instead
[7] Luhman 2001[152]: stated that not clinically apparent aspiration occurred in any patient
[8] Luhman 2001[152]: stated that no cardio respiratory adverse events occurred in any patient at any time
[9] Luhman 2001[152]: no incidents of vomiting in any patient in either group were observed

Table 4: Oral midazolam + non-pharmacological* vs. placebo + non-pharmacological*; Kapur 2004[125]

Love care, Tell show do techniques, physical restrain

Question: Should oral Midazolam plus non-pharmacological technique vs. placebo plus non-pharmacological technique be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?

Settings: dental hospital

Bibliography: Kapur 2004[125] (dental: restorations)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral Midazolam plus non-pharmacological technique	placebo plus non-pharmacological technique	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/20 (90%)	7/20 (35%)	RR 2.57 (1.39 to 4.76)[2]	549 more per 1000 (from 136 more to 1000 more) 0 more per 1,000	LOW	
Duration of procedure (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD -9.83 (-17.22 to -2.44)[4]	VERY LOW	

[1] Kapur 2004[125]: assessors and patients blinded; however unclear allocation concealment, unclear if ITT was performed and dropouts not stated
[2] Kapur 2004[125]: p=0.003
[3] Kapur 2004[125]: wide confidence intervals
[4] Kapur 2004[125]: p=0.009

Table 5: Intranasal midazolam vs. placebo; Fishbein 1997[67]

Question: Should intranasal midazolam vs. placebo be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Fishbein 1997[67] (Venipuncture)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intranasal midazolam	placebo	Relative (95% CI)	Absolute		
Distress – child assessed by an observer using a validated scale (OBRS)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/19 (78.9%)	16/19 (84.2%)	RR 0.94 (0.69 to 1.27)[3]	51 fewer per 1000 (from 261 fewer to 227 more) 0 fewer per 1,000	LOW	

[1] Fishbein 1997[67]: unclear allocation concealment; not true ITT performed -available case analysis only; otherwise double blind and low dropout (<20%) (venipuncture was not performed in 1 patient in each group but reasons not stated)
[2] Fishbein 1997[67]: wide confidence intervals
[3] Fishbein 1997[67]: p=0.68

Table 6: Intranasal midazolam vs. placebo; Ljungman 2000[149], Theroux 1993[212]

Question: Should intranasal midazolam vs. placebo (with local anaesthesia in both arms) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: A & E and oncology
Bibliography: Theroux 1993[212] (suturing for laceration repair) Ljungman 2000[149] (cross over) (needle insertion)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intranasal midazolam plus analgesia	placebo plus analgesia	Relative (95% CI)	Absolute		
Parent satisfaction (Theroux 1993[212])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/22 (68.2%)	9/27 (33.3%)	RR 2.05 (1.12 to 3.75)[3]	350 more per 1000 (from 40 more to 916 more) 0 more per 1,000	LOW	
Patients' preference (Ljungman 2000[149])												
1	randomised trial	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/15 (20%)[6]	0/10 (0%)	RR 4.81 (0.28 to 84.2)[7]	0 more per 1000 (from 0 fewer to 0 more) 0 more per 1,000	VERY LOW	
Parents' preference (Ljungman 2000[149])												
1	randomised trial	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	13/27 (48.1%)	0/22 (0%)	RR 22.18 (1.39 to 353.32)[8]	0 more per 1000 (from 0 more to 0 more) 0 more per 1,000	LOW	
Pain - assessed by parents using a validated scale (measured with: Visual analogue scale; range of scores: 1-100; Better indicated by less) (Ljungman 2000[149])												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[9,10]	none	22	27	-	not pooled	LOW	
Pain - assessed by patients using a validated scale (measured with: Visual analogue scale; range of scores: 1-100; Better indicated by less) (Ljungman 2000[149])												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[10,11]	none	22	27	-	not pooled	LOW	
Adverse events: Vomiting after discharge (Theroux 1993[212])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[12]	none	0/22 (0%)[12]	0/27 (0%)	not pooled	-	LOW	

[1] Theroux 1993[212]: ITT appeared to have been performed and no dropouts were reported; however unclear allocation concealment and blinding of patients and assessors was partially possible only: the control group received no treatment while intervention and placebo groups blinded
[2] Theroux 1993[212]: wide confidence intervals
[3] Theroux 1993[212]: p=0.02
[4] Ljungman 2000[149]: patients and assessors blinded; however, unclear allocation concealment, ITT not performed -available case analysis for the outcomes of pain and patient's preference-

and large amount (>20%) of loss of follow up at interview questionnaires for the outcomes of pain and preference; >35% of parents (25/74) and children (49/74) not contacted for the outcome of preference; for the outcome of pain, 38% (25/74) of children and 3% (2/74) of parents were not contacted

[5] Ljungman 2000[149]: very wide confidence intervals

[6] Ljugman 2000[149]: information/data available from only 25 parents/children; 15 in the first visit and 10 in the second visit

[7] Ljungman 2000[149]: p=0.28

[8] Ljungman 2000[149]: p=0.03

[9] Ljungman 2000[149]: point estimate not possible to calculate based on reported data. Study stated that pain assessed by parents was significantly less in the placebo group (median 81, IQR 46.7 to 92) than the intranasal midazolam (median 90, IQR 76.3 to 98; p=0.39)

[10] Ljungman 2000[149]: median and IQR indicatives of skewed data

[11] Ljungman 2000[149]: point estimate not possible to calculate based on reported data. Study stated that pain assessed by patients was no significant between groups; placebo group (median 87, IQR 41to 97), intranasal midazolam (median 87.5, IQR 78.3 to 100; p=0.625)

[12] Theroux 1993[212]: there was no evidence of any children having vomited after discharge; vomiting was included as part of the follow up data collected from parents by telephone interview

HEAD TO HEAD COMPARISON

Table 7: Oral midazolam vs. oral triclofos sodium; Singh 2002[205]

Question: Should oral midazolam vs. oral triclofos sodium be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Singh 2002[205]

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam	oral triclofos sodium	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/30 (100%)[2]	30/30 (100%)	RR=1	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) 0 fewer per 1,000	LOW	
Recovery (when the patient was able to sit or stand alone with minimal assistance; Better indicated by less)												
1	randomised trial	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD -38.23 (-44.94 to -31.52)	LOW	
Length of induction (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD -16.10 (-18.11 to -14.09)	LOW	

[1] Singh 2002[205]: patients and outcome assessors blinded however concealment, ITT and attrition details not stated
[2] Singh 2002[205]: all completed - ease of treatment completion rated as 1-excellent, 2-difficult and 3-impossible; study stated that treatment was most convenient for midazolam group than for triclofos group. Difficulty in treatment was significantly more for group of promethazine than for midazolam ($p<0.01$) and for triclofos ($p<0.05$)

Table 8: Sublingual midazolam vs. oral chloral hydrate; Layangool 2008[136]

Question: Should sublingual midazolam vs. oral chloral hydrate be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: Outpatients' cardiology unit
Bibliography: Layangool 2008[136] (echocardiogram)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	sublingual midazolam	oral chloral hydrate	Relative (95% CI)	Absolute		
Completion of procedure (number of patients)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	127/132 (96.2%)	131/132 (99.2%)	RR 0.97 (0.93 to 1.01)[3]	30 fewer per 1000 (from 69 fewer to 10 more)	VERY LOW	
Induction time (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	131	-	MD -13.80 (-17.56 to -10.04)[4]	LOW	
Duration of procedure (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	131	-	MD -0.40 (-1.59 to 0.79)[5]	LOW	
Total time (Better indicated by less) Total time covered from administration to recovery in full, determined by vital signs, oxygen saturation and conscious level which were monitored until the child status showed full recovery.												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	131	-	MD 38.80 (33.18 to 44.42)[6]	LOW	
Adverse events: Vomiting												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	1/132 (0.8%)	14/132 (10.6%)	RR 0.07 (0.01 to 0.54)[8]	99 fewer per 1000 (from 49 fewer to 105 fewer)	LOW	
								0.8%		7 fewer per 1,000		

[1] Layangool 2008[136]: stated as double blinded study; however, partial allocation concealment and ITT not performed, available case analysis instead for children who both completed procedure in full plus children who completed procedure partially; and <20% lost of follow up
[2] Layangool 2008[136]: crosses left precision limit
[3] Layangool 2008[136]: p=0.10
[4] Layangool 2008[136]: P<0.00001
[5] Layangool 2008[136]: p=0.51
[6] Layangool 2008[136]: p<0.00001
[7] Layangool 2008[136]: precise
[8] Layangool 2008[136]: p=0.01

Note: For Layangool[136], the ability to complete the procedure was described in four different levels. Level 0 was defined as ‘unable to perform the study’; level 1 was stated as ‘important part of the study accomplished, but study shortened’; level 2 defined a ‘complete study possible with coaxing’; and level 3 was defined as ‘complete study easily accomplished’. Furthermore, the RCT stated that procedure was incompletely performed in four cases in the midazolam group and it was failed in one case in each group. Thus we dichotomised the four levels into procedure completely performed (level 2 + level 3) and procedure not or partly performed (level 0 and level 1).

Table 9: Rectal midazolam + non-pharmacological intervention* versus nitrous oxide (70%) + non-pharmacological intervention*; Zier 2008[239]

**distraction: storytelling, soothing discourse*
Question: Should rectal midazolam vs. nitrous oxide (with topical anaesthesia in both arms) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Zier 2008[239] (injections for spasticity)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rectal midazolam plus placebo plus topical anaesthesia plus non-pharmacological intervention	nitrous oxide plus placebo plus topical anaesthesia plus non-pharmacological intervention	Relative (95% CI)	Absolute		
Pain - number of patients - assessed by a trained observer using a validated scale (Face, Legs, Activity, Cry, Consolability (FLACC))												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	25	-	not pooled[2]-	MODERATE	
Parents satisfaction assessed on a 1 to 10 scale (measured with: arbitrary scale; range of scores: 1-10; Better indicated by less)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22	25	-	not pooled[4]	MODERATE	
Total time (Better indicated by less)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[5]	none	24	25	-	not pooled[5]	MODERATE	
Adverse events: Vomiting during drug nitrous oxide administration												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2,6]	none	0/25 (0%)	4/25 (16%)	RR 0.11 (0.01 to 1.96)[7]	142 fewer per 1000 (from 158 fewer to 154 more) 0 fewer per 1,000	MODERATE	

[1] Zier 2008[239]: adequate concealment, ITT appeared to be performed and there were no loss of follow up reported, adequate allocation concealment and both patients and outcome assessors were blind
[2] Zier 2008[239]: reported p-value=0.010; sample size small; median scores were 6 for the midazolam group and 4 for the nitrous oxide group
[3] Zier 2008[239]: reported satisfaction was no significant between groups; p=0.10; assessed on a 1 to 10 arbitrary scale where 1=satisfaction and 10=dissatisfaction; median scores were 2 for the midazolam group and 1 for the nitrous oxide group; small study
[4] Zier 2008[239]: reported p=0.10
[5] Zier 2008[239]: stated that there was no difference between groups regarding the time each group stayed in the clinic, did not report p-value; small study
[6] Zier 2008[239]: very wide confidence intervals
[7] Zier 2008[239]: p=0.13

COMBINATION COMPARISONS

Table 10: Oral midazolam vs. oral midazolam + nitrous oxide; Al-Zahrani 2009[13]

Question: Should oral midazolam vs. oral midazolam plus nitrous oxide/oxygen (with topical and local anaesthesia in both arms) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Al-Zahrani 2009[13] (dental restorative procedures)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam plus topical anaesthesia plus local anaesthesia	oral midazolam plus nitrous oxide/oxygen plus topical anaesthesia plus local anaesthesia	Relative (95% CI)	Absolute		
Completion of procedure (number of patients)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	30/30 (100%)	30/30 (100%)	RR=1	-	LOW	
Induction time (measured with: minutes; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD -0.70 (-2.59 to 1.19)[4]	LOW	
Duration of procedure (time from bringing the patient to the operating room until the planned dental procedures were completed Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	30	30	-	MD 0.10 (-2.79 to 2.99)[6]	VERY LOW	

[1] Al-Zahrani 2009[13]: cross-over trial, unclear concealment, unclear blinding of outcome assessors but all patients completed the trial and all patients appeared to be included in analyses
[2] Al-Zahrani 2009[13]: imprecise as crosses left precision limit; small sample
[3] Al-Zahrani 2009: small sample
[4] Al-Zahrani 2009[13]: p=0.47
[5] Al-Zahrani 2009[13]: imprecise, crosses right precision limit and very wide confidence intervals; small sample
[6] Al-Zahrani 2009[13]: p=0.95

Note: For Alzahrani (2009), the completion of procedure was based on assessment of overall behaviour using the Houpt scoring system (sleep, crying, movement, behaviour), most of the patients movement did not interrupt dental treatment on both visits and most of the patients showed good or very good behaviour in both groups; with no poor behaviour or treatment aborted.

Table 11: Oral midazolam + nitrous oxide vs. nitrous oxide + placebo; Luhman 2001[152]

Question: Should oral midazolam plus nitrous oxide vs. nitrous oxide plus placebo (with local anaesthesia in both arms) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: accidents and emergencies
Bibliography: Luhman 2001[152] (suturing and laceration repairs)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam plus nitrous oxide plus analgesia	nitrous oxide plus placebo plus analgesia	Relative (95% CI)	Absolute	Quality	
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	52/52 (100%)	51/51 (100%)	RR=1	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) 0 fewer per 1,000	MODERATE	
Adverse events: Aspiration												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/52 (0%)[3]	0/51 (0%)	not pooled	-	MODERATE	
Adverse events: Respiratory intervention												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/52 (0%)[4]	0/51 (0%)	not pooled	-	MODERATE	
Adverse events: Vomiting												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	1/52 (1.9%)	5/51 (9.8%)	RR 0.20 (0.02 to 1.62)[6]	78 fewer per 1000 (from 96 fewer to 61 more) 0 fewer per 1,000	LOW	

[1] Luhman 2001[152]: adequate concealment and low loss of follow up; however single blind study (only assessors were blind) and ITT was not performed
[2] Luhman 2001[152]: not estimable, all patients completed the procedure
[3] Luhman 2001[152]: stated that not clinically apparent aspiration occurred in any patient
[4] Luhman 2001[152]: stated that no cardio respiratory adverse events occurred in any patient at any time
[5] Luhman 2001[152]: wide confidence intervals
[6] Luhman 2001[152]: p=0.13

Table 12: Oral midazolam + intravenous propofol vs. intravenous propofol; Paspatis 2006[178]

Question: Should oral midazolam plus intravenous propofol vs. intravenous propofol (with local anaesthesia in both arms) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Paspatis 2006[178] (endoscopy)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam plus intravenous propofol	intravenous propofol	Relative (95% CI)	Absolute		
Duration of procedure (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	28	-	MD 0.10 (-2.5 to 2.7)[3]	LOW	
Recovery from completion of procedure to recovery/discharge criteria met (measured with: REACT score; range of scores: 0-10; Better indicated by more)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	28	-	MD 18.20 (16.14 to 20.26)[4]	MODERATE	

[1] Paspatis 2006[178]: ITT appeared to have been performed and no loss of follow up were reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear
[2] Paspatis 2006[178]: wide confidence intervals
[3] P=0.94
[4] P<0.00001

Table 13: Intravenous midazolam + intravenous propofol vs. intravenous propofol; Disma 2005[56]

Question: Should intravenous midazolam plus intravenous propofol vs. intravenous propofol be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Disma 2005[56] (Endoscopy)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous midazolam plus intravenous propofol	intravenous propofol	Relative (95% CI)	Absolute		
Completion of procedure (number of patients)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	78/78 (100%)	80/80 (100%)	RR=1	-	MODERATE	
Duration of procedure (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78	80	-	MD -0.20 (-0.98 to 0.58)[4]	MODERATE	
Recovery from completion of procedure to recovery/discharge criteria met (better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	78	80	-	MD 2.50 (-0.4 to 5.4)[5]	LOW	
Adverse events: Assisted ventilation (bag-valve mask)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	0/78 (0%)	5/80 (6.3%)	RR 0.09 (0.01 to 1.66)[7]	57 fewer per 1000 (from 62 fewer to 42 more) 0 fewer per 1,000	LOW	
Adverse events: Oxygen desaturation <90%												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	2/78 (2.6%)	3/80 (3.8%)	RR 0.68 (0.12 to 3.98)[3]	12 fewer per 1000 (from 33 fewer to 113 more)	LOW	

[1] Disma 2005[56]: ITT appeared to be performed and there were no loss of follow up reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear
[2] Disma 2005[56]: wide confidence intervals
[3] P=0.67
[4] P=0.62
[5] P=0.09
[6] Disma 2005[56]: wide confidence intervals
[7] P=0.11

Table 14: Intravenous midazolam + intravenous meperidine vs. intravenous meperidine; Fishbein 1997[67]

Question: Should intravenous midazolam plus intravenous meperidine vs. intravenous meperidine be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Fishbein 1997[67] (esophagogastroduodenoscopy)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous midazolam plus intravenous meperidine	placebo plus intravenous meperidine	Relative (95% CI)	Absolute		
Distress assessed by an observer using a validated scale (Observational Behaviour Rating Scale (OBRS) - data for major behaviours)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	18/20 (90%)	19/20 (95%)	RR 0.95 (0.79 to 1.13)[3]	48 fewer per 1000 (from 199 fewer to 123 more) 0 fewer per 1,000	MODERATE	
Duration of procedure (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	20	20	-	MD 0.40 (-1.22 to 2.02)[5]	LOW	

[1] Fishbein 1997[67]: unclear allocation concealment; not true ITT performed -available case analysis only; otherwise double blind and low dropout (<20%) (venipuncture was not performed in 1 patient in each group but reasons not stated)
[2] Fishbein 1997[67]: precise
[3] Fishbein 1997[67]: p=0.55
[4] Fishbein 1997[67]: imprecise
[5] Fishbein 1997[67]: p=0.63

Table 15: Intravenous midazolam + intravenous morphine vs. intravenous propofol + intravenous morphine + local anaesthesia; Havel 1999[91]

Question: Should intravenous midazolam plus intravenous morphine vs. intravenous propofol plus intravenous morphine plus local anaesthesia (with placebo in both groups) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: accidents and emergencies
Bibliography: Havel 1999[91] (fractures of the forearm, humerus, femur, lower leg, or hand, hip dislocation)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous midazolam plus intravenous morphine plus placebo	intravenous propofol plus intravenous morphine plus placebo plus lidocaine	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/46 (100%)	43/43 (100%)	not estimable 0 (0 to 0)[2]	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) 0 fewer per 1,000	LOW	
Induction time (better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	53	-	MD 0.20 (-1.89 to 2.29)[3]	LOW	
Duration of procedure (better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	43	-	MD 0.70 (-5.34 to 6.74)[4]	LOW	
Pain (number of patients who reported pain)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/46 (4.3%)	3/43 (0%)	RR 0.61 (0.1 to 3.82)[6]	0 fewer per 1,000	VERY LOW	
Recovery time (better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	43	-	MD 46.80 (40.76 to 52.84)[7]	LOW	
Total time (from admission until having been discharged from the clinic; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	43	-	MD 23.80 (0.93 to 46.67)	LOW	
Adverse events: Aspiration												
1	randomised	very	no serious	no serious	no serious	none	0/46 (0%)[8]	0/43 (0%)	RR=1	not pooled[8]-		

	trial	serious[1]	inconsistency	indirectness	imprecision[8]					-	LOW	
Adverse events: Assisted ventilation												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[9]	none	0/46 (0%)[9]	0/43 (0%)	RR=1	not pooled[9]	LOW	
Adverse events: Endotracheal intubation												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/46 (0%)	0/43 (0%)	RR=1	not pooled not pooled	LOW	
								0/43 (0%)	RR=1	not pooled[8]-	VERY LOW	
										-		

[1] Havel 1999[91]: patients and outcome assessors were blind and low loss of follow-up; however, inadequate allocation concealment, the sedationist knew medications, infusion tubing and intravenous site and ITT was not performed -per protocol analysis instead
[2] Havel 1999[91]: not estimable; all patients completed the procedure
[3] Havel 1999[91]: p=0.85
[4] Havel 1999[91]: p=0.82
[5] Havel 1999[91]: crosses both confidence limits
[6] Havel 1999[91]: p=0.59
[7] Havel 1999[91]: p<0.00001
[8] Havel 1999[91]: stated that not clinically apparent aspiration occurred in any patient in either sedation group
[9] Havel 1999[91]: no patient in either sedation group required assisted ventilation

Table 16: Intravenous midazolam + intravenous afentanil vs. intravenous afentanil; Antmen 2005[16]

Question: Should intravenous midazolam plus intravenous afentanil vs. intravenous afentanil be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: paediatric haematology outpatients
Bibliography: Antmen 2005[16] (bone marrow aspiration)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous midazolam plus intravenous afentanil	intravenous afentanil	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/20 (100%)	20/20 (100%)	not estimable	-	LOW	
Pain assessed by the anaesthetist using a validated scale - 2 (measured with: Children's Hospital of Eastern Ontario Pain Scale (CHEOPS); range of scores: 0-13; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD -0.15 (-1.05 to 0.75)	VERY LOW	
Pain assessed by the anaesthetist using a validated scale - 1 (measured with: Visual analogue scale (VAS); range of scores: 0-10; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD -0.30 (-1.8 to 1.2)	VERY LOW	
Adverse events: Oxygen desaturation <90%												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	RR=1	not pooled -	LOW	
Adverse events: Vomiting												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	RR=1	not pooled -	LOW	

[1] Antmen 2005[16]: ITT appeared to be performed and there were no loss of follow up reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear; small study N=20
[2] Antmen 2005[16]: confidence intervals cross precision limits

Table 17: Intravenous midazolam + intravenous remifentanil vs. intravenous remifentanil; Antmen 2005[16]

Question: Should intravenous midazolam plus intravenous remifentanil vs. intravenous remifentanil be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: paediatric haematology outpatients
Bibliography: Antment 2005[16] (bone marrow aspiration)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous midazolam plus intravenous remifentanil	intravenous remifentanil	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/20 (100%)	20/20 (100%)	RR=1	-	LOW	
Pain assessed by the anaesthetist using a validated scale - 2 (measured with: Children's Hospital of Eastern Ontario Pain Scale (CHEOPS); range of scores: 0-13; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD -0.05 (-0.68 to 0.58)[3]	VERY LOW	
Pain assessed by the anaesthetist using a validated scale - 1 (measured with: Visual Analogue Scale (VAS); range of scores: 0-10; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD -0.05 (-0.86 to 0.76)	VERY LOW	
Adverse events: Oxygen desaturation <90%												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	RR=1	- not pooled	LOW	
Adverse events: Vomiting												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	RR=1	not pooled -	LOW	

[1] Antmen 2005[16]: ITT appeared to be performed and there were no loss of follow up reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear; small study N=20
[2] Antmen 2005[16]: confidence intervals cross precision limits
[3] Antmen 2005[16]: p=0.88

Table 18: Intravenous midazolam + intravenous ketamine vs. intravenous ketamine + placebo; Sherwin 2000[203]; Wathen 2000[229]; Dilli 2008[55]

Question: Should intravenous midazolam plus intravenous ketamine vs. intravenous ketamine plus placebo be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: A & E and hospital outpatients
Bibliography: Wathen 2000[229] (fractures, lacerations, other including joint aspiration, abscess drainage, vaginal laceration, dog bite, wound care, chest tube placement, nail bed injury, vaginal foreign body removal, inguinal hernia, urologic procedures); Sherwin 2000[203] (intravenous catheter insertion for orthopaedic, wound or thermal, other procedures) Dilli 2008[55] (lumbar puncture)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**efficacy of intravenous midazolam plus intravenous ketamine**	**intravenous ketamine plus placebo**	**Relative (95% CI)**	**Absolute**		
Completion of procedure (Sherwin 2000[203]; Wathen 2000[229])												
2	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision[3,4]	none	190/190 (100%)	180/180 (0%)	not estimable	-	MODERATE	
Induction time (Better indicated by less) (Dilli 2008[55])												
1	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	48	51	-	MD -0.80 (-1.36 to -0.24)	VERY LOW	
Parents' satisfaction (Dilli 2008[55])												
1	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	-	-	p=0.001[7]	-	LOW	
Recovery time (Better indicated by less) (Dilli 2008[55])												
1	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	48	51	-	MD 2.20 (-0.79 to 5.19)	VERY LOW	
Parents' satisfaction (Wathen 2000[229])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/137 (81.8%)	115/129 (89.1%)	RR 0.92 (0.83 to 1.01)	71 fewer per 1000 (from 151 fewer to 9 more) 0 fewer per 1,000	MODERATE	
Duration of procedure (Better indicated by less) (Wathen 2000[229])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	112	115	-	MD -1(IQR, 95% CI -5 to 1)	LOW	

[1] Wathen 2000[229]: adequate allocation concealment and patients and assessors were blinded; however, ITT was not performed -per protocol analysis instead; low amount of loss of follow up: 3 randomised patients dropped out, 2 in the intervention and 1 in the control group had protocol violation and received intramuscular vial instead of intravenous
[2] Sherwin 2000[203]: adequate allocation concealment and patients and were blinded, ITT appeared to have been performed and there were no loss of follow up reported
[3] Wathen 2000[229]: not estimable, all patients completed the procedure
[4] Sherwin 2000[203]: not estimable, all patients completed the procedure
[5] Dilli 2008[55]: adequate allocation concealment, and outcome blinded; however ITT was not performed -per protocol analysis instead: 104 randomised but 99 analysed: midazolam+ketamine=48, ketamine=51; loss of follow up: midazolam+ketamine group: 4%(2/50) one patient did not received allocated intervention and one was lost to follow-up; 6%(3/54) one patient did not received allocated intervention and two were lost to follow-up; patients were not blind
[6] Dilli 2008*[55]: crosses left confidence limit
[7] Dilli 2008[55]: stated that parental satisfaction was significantly higher in patients in the midazolam group, p=0.001
[8] Dilli 2008[55]: crosses right confidence limit
[9] Wathen 2000[229]: the study stated that the difference between ketamine+midazolam versus ketamine plus placebo was no significant; mean difference -1 minute (IQR, 95% CI-5 to 1)
*Note: Dilli[55], also stated that patients were discharged two hours after procedure and after being awake, coherent and able to tolerate oral food

Table 19: Safety of intravenous midazolam + intravenous ketamine vs. intravenous ketamine + placebo

Question: What is the safety of intravenous midazolam plus intravenous ketamine vs. intravenous ketamine plus placebo in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: A & E and hospital outpatients
Bibliography: Wathen 2000[229] (fractures, lacerations, other including joint aspiration, abscess drainage, vaginal laceration, dog bite, wound care, chest tube placement, nail bed injury, vaginal foreign body removal, inguinal hernia, urologic procedures); Sherwin 2000[203] (intravenous catheter insertion for orthopaedic, wound, thermal injury or other procedures) Dilli 2008[55] (lumbar puncture)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	adverse events of intravenous midazolam plus intravenous ketamine	intravenous ketamine plus placebo	Relative (95% CI)	Absolute		
Adverse events: Vomiting (during visit and at home 12 hrs after discharge and well into recovery) (Wathen 2000[229]; Sherwin 2000[203])												
2	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3,4]	none	14/190 (7.4%)	31/180 (17.2%)	RR 0.43 (0.24 to 0.77)[5]	98 fewer per 1000 (from 40 fewer to 131 fewer) 0 fewer per 1,000	LOW	
Adverse events: Assisted ventilation (bag mask) (Sherwin 2000[203]; Wathen 2000[229])												
2	randomised trial	no serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[6]	none	1/190 (0.5%)	1/180 (0.6%)	RR 0.94 (0.06 to 14.9)[9]	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1,000	LOW	
Adverse events: Aspiration (Wathen 2000; Sherwin 2000[203])												
2	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/190 (100%)[7]	0/180 (100%)[7]	RR=1	not pooled -	MODERATE	
Adverse events: Endotracheal intubation (Wathen 2000[229])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	0/137 (100%)[8]	0/129 (100%)[8]	RR=1	- not pooled	MODERATE	
Adverse events: Oxygen desaturation 90% (Wathen 2000[229]; Sherwin 2000[203]; Dilli 2008[55])												
3	randomised trial	very serious[1,2,10]	no serious inconsistency[11]	no serious indirectness	no serious imprecision	none	14/238 (5.9%)	3/231 (1.3%)	RR 4.01 (1.27 to 12.68)[12]	39 more per 1000 (from 4 more to 152 more) 0 more per 1,000	LOW	

[1] Wathen 2000[229]: adequate allocation concealment and patients and assessors were blinded; however, ITT was not performed -per protocol analysis instead; low amount of loss of follow up: 3 randomised patients dropped out, 2 in the intervention and 1 in the control group had protocol violation and received intramuscular vial instead of intravenous
[2] Sherwin 2000[203]: adequate allocation concealment and patients and assessors were blinded, ITT appeared to have been performed and there were no loss of follow up reported
[3] Wathen 2000[229]: very wide confidence intervals
[4] imprecise: cross left precision limits

5 Wathen 2000[229] and Sherwin 2000[203]: p=0.005
6 Sherwin 2000[203];Wathen 2000[229]: imprecise, wide confidence intervals; no assisted ventilation was required in any patients in either group in the study by Sherwin[203] while one patient in each group required assisted ventilation in the study by Wathen[229]
7 Wathen 2000[229] and Sherwin 2000[203]: there was no incidence of aspiration in any patient in either group
8 Wathen 2000[229]: stated that endotracheal intubation was not performed in any patient
9 Wathen 2000[229]: p=0.97
10 Dilli 2008[55]: adequate allocation concealment, and outcome assessors blinded; however ITT was not performed -per protocol analysis instead: 104 randomised but 99 analysed: midazolam+ketamine=48, ketamine=51; loss of follow up: midazolam+ketamine group: 4%(2/50) one patient did not received allocated intervention and one was lost to follow-up; 6%(3/54) one patient did not received allocated intervention and two were lost to follow-up; patients were not blind
11 Wathen 2000[229], Sherwin 2000[203] and Dilli 2008[55]: not significant heterogeneity=0%, p=0.53
12 Wathen 2000[229], Sherwin 2000[203] and Dilli 2008[55]: p=0.02

ROUTE OF ADMINISTRATION COMPARISONS

Table 20: Oral midazolam vs. intranasal midazolam; Connors 1994[42]; Everitt 2002[60]

Question: Should oral midazolam vs. intranasal midazolam be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: accidents and emergencies
Bibliography: Connors 1994[42] (suturing for laceration repair) Everitt 2002[60] (suturing for laceration repair)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam	intranasal midazolam	Relative (95% CI)	Absolute		
Completion of procedure (Connors 1994[42])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/26 (100%)	28/28 (100%)	RR=1	-	MODERATE	
Distress assessed by an observer using a validated scale (measured with VAS; range of scores: 1-100; Better indicated by less) (Everitt 2002[60])												
1	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	45	42	-	MD -13 (-25.83 to -0.17)[4]	VERY LOW	
Total time: administration to recovery area/discharge criteria (measured with: minutes; Better indicated by less) (Connors 1994[42]; Everitt 2002[60])												
1	randomised trial	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	71	70	-	MD 3 (-1.44 to 7.44)[5]	VERY LOW	

[1] Connors 1994[42]: double blind (patients and outcome assessors), double placebo trial with low loss of follow up: 7% (4/58) of patients were excluded from analyses (2 in each group had protocol violation and for 2 data collection was not available); however, allocation concealment was not stated and ITT was not performed -per protocol analysis instead; small study
[2] Everitt 2002[60]: unclear allocation concealment, outcome assessors partially blinded (assessors: staff participating were unaware of sedative being given but parents who also assessed children for anxiety were aware of sedative given), ITT and amount of loss of follow up were unclear or not stated; also, study stated to have obtained data on parents' satisfaction after discharge but results data were not reported (selective outcome reporting)
[3] Everitt 2002[60]: imprecise; wide confidence intervals
[4] Everitt 2002[60]: p=0.05
[5] Everitt 2002[60]: p=1.00
[6] Everitt 2002[60]: selective

Table 21: Oral midazolam + nitrous oxide (40/45%) vs. intranasal midazolam+ nitrous oxide (40/45%); Hartgraves 1994[90]; Lee-Kim 2004[138]

Question: Should oral midazolam plus nitrous oxide vs. intranasal midazolam plus nitrous oxide (with local anaesthesia in both groups) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Hartgraves 1994[90]; Lee-Kim 2004[138]

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral midazolam plus nitrous oxide plus lidocaine	intranasal midazolam plus nitrous oxide plus lidocaine	Relative (95% CI)	Absolute		
Completion of procedure (Hartgraves 1994[90])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	45/50 (90%)	47/50 (94%)	RR 0.96 (0.85 to 1.08)[3]	38 fewer per 1000 (from 141 fewer to 75 more) 0 fewer per 1,000	LOW	
Induction time (Better indicated by less) (Lee-Kim 2004[138])												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	20	20	-	MD 9.95 (7.56 to 12.34)[6]	MODERATE	
Total time (from administration to recovery area/discharge criteria -defined as drugs working time) (Lee-Kim 2004[138])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	20	20	-	MD 8.80 (2.73 to 14.87)[9]	LOW	
Adverse events: Oxygen desaturation <90% (Hartgraves 1994[90])												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	2/50 (4%)	1/50 (2%)	RR 2 (0.19 to 21.36)[10]	20 more per 1000 (from 16 fewer to 407 more) 0 more per 1,000	VERY LOW	

[1] Hartgraves 1994[90]: allocation concealment not stated, blinding of assessors was unclear and patients not blinded; also, it was unclear whether ITT was performed and unclear loss of follow up
[2] Hartgraves 1994[90]: precise
[3] Hartgraves 1994[90]: p=0.46
[4] Lee-Kim 2004[138]: assessors were blinded, ITT appeared to have been performed and no loss of follow up were reported; however, unclear allocation concealment and patients were not blinded
[5] Lee-Kim 2004[138]: precise
[6] Lee-Kim 2004[138]: p<0.00001
[7] Lee-Kim 2004[138]: imprecise, wide confidence intervals
[8]Hartgraves 1994[90]: imprecise, very wide confidence intervals

[9] Lee-Kim 2004[138]; p=0.005
[10] Hartgraves 1994[90]: p=0.57

Table 22: Intranasal midazolam vs. intramuscular midazolam; Shashikiran 2006[202]

Question: Should intranasal midazolam vs. intramuscular midazolam (with analgesia in both groups) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Sashikiran 2006[202] (dental)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intranasal midazolam plus analgesia	intramuscular midazolam plus analgesia	Relative (95% CI)	Absolute		
Induction time (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	20	20	-	MD -4.90 (-6.14 to -3.66)[3]	MODERATE	
Recovery from completion of procedure to recovery/discharge criteria met (better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	20	20	-	MD -24.40 (-26.48 to -22.32)[3,4]	MODERATE	
Adverse events: Vomiting												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	0/20 (0%)[5]	0/20 (0%)	RR=1	- not pooled	MODERATE	

[1] Sashikran 2006[202]: ITT appeared to have been performed and no loss of follow up were reported; however, unclear allocation concealment, blinding of outcomes assessors was unclear and patients were not blinded
[2] Sashikran 2006[202]: precise
[3] Sashikran 2006[202]: p<00001
[4] Sashikran 2006[202]: p<00001
[5] Sashikran 2006[202]: stated that there was not a single incidence of vomiting

DOSE COMPARISONS

Table 23: Intranasal midazolam 0.3mg/kg + nitrous oxide vs. intranasal midazolam 0.2 mg/kg + nitrous oxide; Fuks 1994[71]; Fukuta 1994[72]

Question: Should intranasal midazolam 0.3 mg/kg plus nitrous oxide vs. intranasal midazolam 0.2 mg/kg plus nitrous oxide be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Fuks 1994[71] (dental restorations); Fukuta 1994[72] (dental restorations)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	efficacy of intranasal midazolam 0.3 mg/kg plus nitrous oxide	intranasal midazolam 0.2 mg/kg plus nitrous oxide	Relative (95% CI)	Absolute		
Completion of Procedure (Fuks 1994[71] - cross over)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	30/30 (100%)	30/30 (100%)	RR=1	-	MODERATE	
Completion of Procedure (Fukuta 1994[72] - parallel)												
1	randomised trial	serious	no serious inconsistency	no serious indirectness	serious	none	20/21 (95.2%)	16/22 (72.7%)	RR 1.31 (1 to 1.72)	225 more per 1000 (from 0 more to 523 more) 0 more per 1,000	LOW	
Duration of procedure (Better indicated by more)(Fukuta 1994[72])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[4,5]	none	20	22	-	MD 0.60 (-7.23 to 8.43)[6,7]	LOW	

[1] Fuks 1994[71]: assessors were blind, ITT appeared to be performed and no loss of follow up were reported; however, allocation concealment was unclear and blinding of patients was not stated
[2] Fuks 1994[71]: not estimable, all patients completed the procedure
[3] Fukuta 1994[72]: patients and assessors were blind, ITT appeared to have been performed and no loss of follow up were reported; however, allocation concealment was not stated
[4] Fukuta 1994[72]: imprecise
[5] Fukuta 1994[72]: imprecise; very wide confidence intervals
[6] Fukuta 1994[72]: p=0.05
[7] Fukuta 1994[72]: p=0.88

Table 24: Safety of intranasal midazolam 0.3 mg/kg plus nitrous oxide vs. intranasal midazolam 0.2 mg/kg plus nitrous oxide

Question: What is the safety of intranasal midazolam 0.3 mg/kg plus nitrous oxide vs. intranasal midazolam 0.2 mg/kg plus nitrous oxide in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: dental hospital
Bibliography: Fuks 1994[71] (dental restorations); Fukuta 1994[72] (dental restorations)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	adverse events of intranasal midazolam 0.3 mg/kg plus nitrous oxide	intranasal midazolam 0.2 mg/kg plus nitrous oxide	Relative (95% CI)	Absolute		
Adverse events: Vomiting - (Fuks 1994[71])												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	0/30 (0%)[2]	0/30 (0%)[2]	RR=1	Not pooled-	MODERATE	
Adverse events: Oxygen desaturation <90% (Fukuta 1994[72])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/21 (4.8%)	0/22 (0%)	RR 3.14 (0.13 to 72.96)[5]	0 more per 1000 (from 0 fewer to 0 more) 0 more per 1,000	VERY LOW	
Adverse events: Assisted respiration (during and post dental treatment) (Fukuta 1994[72])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	0/21 (0%)[2]	0/22 (0%)	not pooled	-	MODERATE	
Adverse events: Vomiting during dental procedure (Fukuta 1994[72])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/21 (4.8%)	0/22 (0%)	RR 3.14 (0.13 to 72.96)[5]	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	
Adverse events: Vomiting post dental procedure (Fukuta 1994[72])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/21 (0%)[7]	0/22 (0%)	RR=1	Not pooled-	MODERATE	

[1] Fuks 1994[71]: assessors were blind, ITT appeared to have been performed and no loss of follow up were reported; however, allocation concealment was unclear and blinding of patients was not stated
[2] Fuks 1994[71]: no adverse events such as vomiting were observed
[3] Fukuta 1994[72]: patients and assessors were blind, ITT appeared to have been performed and no loss of follow up were reported; however, allocation concealment was not stated
[4] Fukuta 1994[72]: too wide confidence intervals
[5] Fukuta 1994[72]: p=0.48
[6] Fukuta 1994[72]: stated that no patients needed assisted respiration during and post dental treatment
[7] Fukuta 1994[72]: there were no incidents of vomiting post dental procedure in any patient in either group

Table 25: Rectal midazolam 2mg/kg vs. rectal midazolam 1mg/kg; Kanegaye, 2003[124]

Question: Should rectal midazolam 2mg/kg vs. rectal midazolam 1mg/kg (with local anaesthesia in both groups) be used in children and young people under 19 years of age undergoing diagnostic and therapeutic procedures?
Settings: accidents and emergencies
Bibliography: Kanegaye 2003[124] (suturing for laceration repair)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rectal midazolam 2mg/kg plus lidocaine**	**rectal midazolam 1mg/kg plus lidocaine**	**Relative (95% CI)**	**Absolute**		
Parents' satisfaction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/28 (85.7%)	18/26 (69.2%)	RR 1.24 (0.92 to 1.67)[3]	166 more per 1000 (from 55 fewer to 464 more) 0 more per 1,000	LOW	
Total time: from administration to recovery/discharge criteria (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	33	32	-	MD 6 (-9.35 to 21.35)[5]	LOW	
Recovery (total recovery time from completion of procedure to recovery/discharge criteria met; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	33	32	-	MD -1 (-15.21 to 13.21)[6]	LOW	
Adverse events: Cardio respiratory complications												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/28 (0%)[7]	0/26 (0%)	RR-1	-not pooled	MODERATE	

[1] Kanegaye 2003[124]: adequate allocation concealment, assessors were blind and some patients were blind; ITT appeared to have been performed for the outcome of recovery and total time; however for the outcome of parents' satisfaction, case analysis was available although loss of follow up was 17% (11/65: 5 in the intervention and 6 in the control groups) due lack of data collection
[2] Kanegaye 2003[124]: imprecise
[3] Kanegaye 2003[124]: p=0.16
[4] Kanegaye 2003[124]: imprecise; wide confidence intervals
[5] Kanegaye 2003[124]: p=0.44
[6] Kanegaye 2003[124]: p=0.89
[7] Kanegaye 2003[124]: stated that no cardio respiratory complications occurred in any patient
[8] Kanegaye 2003[124]: selective outcome reporting: vomiting was part of the outcome data collected but results were not reported

6.3.2.2 Non RCT evidence profiles for safety for midazolam

Seven non RCT observational studies (n=5,412) assessed the safety of midazolam[98,141,157,180,184,190,197]. There were six prospective studies, and one retrospective study conducted for the following procedures: dental (1), imaging procedures (1), accident and emergencies procedures (4) as well for GI procedures (1).

The non RCT study characteristics for midazolam are presented in Table 26.

The non RCT adverse event table for midazolam is presented in Table 27.

NON-RCT OBSERVATIONAL STUDIES FOR MIDAZOLAM

Table 26: Midazolam Non RCT Study Characteristics Safety Review

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Peña 1999, USA[180]	paediatric emergency department for diagnostic imaging, oral and rectal sedation and analgesia. IM and IV in radiology suite	ASA I-II	described as procedural sedation and analgesia (depressed level of consciousness)	62% (733/1188)	IM ketamine+midazolam: 0.01-0.05 mg/kg IV keatmine+midazolam: 0.025-0.05 mg/kg IM or IV atropine 0.02 mg/kg	Not stated
Hulland 2002, Canada[98]	Paediatric outpatients	ASA I-III	Conscious sedation	N2O 53% (126/240) Midazolam 54% (310/579)	Oral midazolam: 0.5 mg/kg max 10 mg per appointment. mean 8.6 mg/kg Nitrous oxide/Oxygen: no higher than 70% concentration	Not stated
PItetti 2003, USA[184]	Accidents and emergencies	81% were Class I; 17% were class II; 1.3% were class III and 0.1% were class IV.	Procedural sedation	65.1% boys in total sample (791)	IV fentanyl citrate + midazolam & IV morphine sulphate + midazolam and IV midazolam Mean fentanyl dose: 2.7 mcg /kg Midazolam 0.1 mg/kg; Morphine not stated	Mean fasting 5.0 + 2.8 hours before sedation.
Roback 2005, USA[191] (*update of	Accidents and emergencies	ASA I-II	described as procedural sedation and analgesia	Iv/im midazolam: 52.7% (137/260)	iv or im midazolam iv or im midazolam (0.1 mg/kg) +	Based upon a population of 2085 children from previous reports, (Roback

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Roback 2004 & follow-up from Wathen 2000)				Iv/im midazolam + ketamine + glycopyrrolate: 56.9% (170/299) Iv/im midazolam + fentanyl 56.8% (191/336) Iv or im ketamine 63.1 (941/1492)	ketamine (1 mg/kg) iv or im midazolam + fentanyl Iv or im ketamine (1mg/kg) (where stated doses were obtained from previous reports*)	2004 and Wathen 2000) up to 8 hrs in 60% more than 8 hrs in 14.5% not documented in 25.4%
Mamula 2007, USA[157]	Operating Room	ASA I-III	Intravenous or general anaesthesia	55% (674/1226)	IV midazolam (2 mg/2mL) & fentanyl (100 mcg/2mL) during 1 minute. Midazolam 0.05 to 0.1 mg/kg max 2 mg; fentanyl 1 mcg/kg max 75 mcg Oral midazolam for anxious patients; IV diphenhydramine as additional drug	3 hours
Sacchetti 2007, USA[197]	Accidents and emergencies prospective observational database	94.1% of total cohort Class I, 5.3% class II and 0.6% class III.	Procedural sedation	Not stated	Fentanyl & Morphine	Not stated
Lightdale, 2009 USA[141]	outside operating room retrospective analysis of a database of clinical and adverse events records of all procedures requiring	Not stated	described as procedural sedation	56% (2,825/5,045)	IV midazolam (N=1,059) IV fentanyl (N=762) Chloral hydrate (N=604) Ketamine (N=513) Meperidine (N=21) Pentobarbital (N=2959)	Not stated

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
	sedation occurring outside of an operating room at a large tertiary care hospital 82% of patients had underlying medical conditions clinical and adverse events recorded by institutionally credentialed nurses				20% (1017/5045) had two drugs in combination	

Table 27: Midazolam Safety: Non RCTs

Study type, reference, country	**Drug / Comparison**	**Procedure**	**Age**	**Total N**	**ADVERSE EVENTS, rate: % (n)**								**GRADE PROFILE**
					Aspiration				**Cardiac arrest requiring either/or**		**vomiting**	**oxygen desaturation <90%**	**EVIDENCE QUALITY**
						oral-pharyngeal airway	**endotracheal intubation**	**assisted ventilation**	**external cardiac massage**	**defibrillation**			
Peña, 1999 USA[180]	IV midazolam + fentanyl	laceration repairs, fracture reduction, CT, abscess drainage laceration repairs fracture reduction, lumbar puncture, bone marrow aspiration, foreign body removal, hernia reduction, arthrocentesis	range (of 1,188 patients): 1 mo-21 y median: 48 mo	391			0%	0.51% (2/391)bag and mask			1.02% (4/391)	2.56% (10/391)	VERY LOW
	IM midazolam + ketamine + atropine			180			0%	0.55% (1/180) bag and mask			0.55% (1/180)	1.11% (2/180)	VERY LOW
	IV midazolam + ketamine + atropine			40			0%				2.5% (1/40)		VERY LOW
	IN midazolam + sufentanyl			25			0%					4% (1/25)	VERY LOW
	inh nitrous oxide			168			0%	0.60% (1/168) bag and mask				0.60% (1/168)	VERY LOW
	IV fentanyl			21			0%						VERY LOW
	IV midazolam +morphine			1			0%						VERY LOW
	oral midazolam			62			0%						VERY LOW

	IN midazolam			3			0%						VERY LOW
	IV midazolam			67			0%						VERY LOW
Hulland, 2002 Canada[98]	oral midazolam	dental	range: 0.9-10.5y mean: 5.4 y	579								1.55% (9/579)	VERY LOW
	Inh nitrous oxide	dental	range: 3-14y mean: 10.8y	240 (326 sedation s)								1.54% (5/326)	VERY LOW
Pltetti 2003, USA[184]	IV fentanyl citrate + midazolam hydrochloride vs. midazolam alone	A & E	0-21 years (of 1244 patients, mean age:6.9 (SD4.5)	686 vs 65 Total adverse events: 23.5% vs. 1.5%			0%						VERY LOW
	IV morphine sulphate + midazolam vs. IV midazolam	A & E	0-21 years (of 1244 patients, mean age:6.9 (SD4.5)	48 vs. 65 Total adverse events: 16.7% vs. 1.5%			0%						VERY LOW
Roback et al, 2005[191]	IV or IM midazolam	fracture reduction, laceration repair, lumbar puncture, imaging, other	range: 42d-32y median: 4.91y	260							0.8% (2/260)		VERY LOW

	IV or IM midazolam + ketamine + glycopyrrolate	fracture reduction, laceration repair, lumbar puncture, imaging, other	range: 4.8mo-18y median: 6.21 y	299							5.4% (16/299)		VERY LOW
	IV or IM midazolam + fentanyl	fracture reduction, laceration repair, lumbar puncture, imaging, other	range: 19d-28y mean: 7.84 y	336							1.8% (6/336)		VERY LOW
	IV or IM ketamine	fracture reduction, laceration repair, lumbar puncture, imaging, other	range 39 days-22 y median 6.85y	1492							10.1% (151/14 92)		VERY LOW
Mamula, 2007 USA[157]	IV midazolam/fenta/ only when needed: oral Mid for anxious children & diphenhydramine to reach desired effect	oesophagogast ro duodenoscopie s colonoscopies and combined	range: 0.1-34 y 4%(55/12 26) were ≥18 years median: 10 y mean: 9.05 y (SD 5.8)	1226	0% (pulmonar y aspiration)		0%	0.16% (2/1226) (bag/mask ventilation)	0% (0/1226) (cardiac arrest)		5.2% (64/122 6) (during recovery)		VERY LOW

Sacchetti 2007, USA[197]	Fentanyl	A & E	0-20 years	51/977 *episode of apnea with fentanyl and etomidate which required reversal was only adverse event reported.									VERY LOW
Lightdale, 2009 USA[141]	IV midazolam (N=1,059) IV fentanyl (N=762) Chloral hydrate (N=604) Ketamine (N=513) Meperidine (N=21) Pentobarbital (N=2959) 20% (1017/5045) had two sedatives in combination	Mixed procedures* 81% (4072/5045) underwent sedation for imaging procedures 48% (2408/5045) underwent MRI; 969 non-imaging procedures were painful and 34 nonpainful	≤30 years old Median age: 3.3 years (IQR 1.4, 6.4) with 75% of children ≤6.4 years old	5,045 &There were 329 adverse events in total 97 AE defined as serious 232 AE defined as minor	0% (serious AE)				0.02% (1/5045) (serious AE) (cardiovascular complications)	0.04% (2/5045) (serious AE) (need for resuscitation)	0.8% (42/5045) (minor AE)		VERY LOW

6.3.3 Evidence statements for midazolam

6.3.3.1 RCT efficacy and safety for midazolam

PLACEBO COMPARISONS or NON-DRUG TREATMENT

Oral midazolam vs. placebo/no drug treatment

For the outcome of completion of procedure, we found evidence of highly significant heterogeneity (I^2=83%; p=0.02) between two RCTs[140,170]. Possible sources of heterogeneity could be attributed to the differences between the studies in procedure performed (dental versus venous placement) and length of procedure (dental is likely to be longer), setting (outpatients versus gastroenterology) and dose [0.25 mg/kg (dental) versus 0.5 mg/kg (for intravenous placement)]. We therefore felt it was not appropriate to pool the RCTs together in a meta-analysis and the studies are presented separately for this outcome.

Mortazavi 2009[170]

Compared with placebo/no drug treatment, the oral midazolam group had significantly:

- More completed procedures [low evidence quality]

There were no events of:

- Oxygen desaturation <90% [low evidence quality]

Liacouras 1998[140]

Compared with placebo/no drug treatment, the oral midazolam group had significantly

- More completed procedures [moderate quality evidence]

There was no significant difference in:

- Duration of procedure [the study stated that and time to discharge were not significant (data was not shown)].

Oral midazolam vs. placebo

Luhman 2001[152]

There were no events of:

- Aspiration [moderate quality evidence]

- Respiratory intervention [moderate quality evidence]
- Vomiting during procedure and recovery [moderate quality evidence]

There was no significant difference in:

- Completion of procedure [moderate quality evidence]

Fatovich 1995[63]

Compared with placebo + analgesia, the oral midazolam + analgesia group were significantly:

- Less distressed (assessed by parents, VAS) [moderate quality evidence]

There was no significant difference in:

- The level of anxiety (Herbertt-Michaelinnees-Venham scale) [moderate quality evidence]

Oral midazolam plus non-pharmacological vs. placebo plus non-pharmacological

Kapur 2004[125]

Compared with placebo + non-pharmacological intervention, the oral midazolam + non-pharmacological intervention had significantly:

- More completed procedures [low quality evidence]
- Shorter duration of procedure [very low quality evidence]

Intranasal midazolam vs. placebo

Fishbein 1997[67]

There was no significant difference in:

- Distress (Observational Behaviour Rating Scale) (OBRS) [low quality evidence]

Intranasal midazolam vs. placebo

Ljungman 2000[149]

Compared with placebo + analgesia, the intranasal midazolam + analgesia group had significantly:

- More parents who preferred midazolam + analgesia [low quality evidence]

There was no significant difference in:

- Patients' preference [very low quality evidence]

Pain assessment:

It was not possible to calculate the point estimate for this outcome based on the data provided. The study gave the median and interquartile ranges with the corresponding p-values indicating a source of bias (spread of skewed or non-normally-distributed data).

- Pain assessed by parents (VAS) [low quality evidence]
- Pain assessed by patients (VAS) [low quality evidence]

Theroux 1993[212]

Compared with placebo + analgesia, the intranasal midazolam + analgesia group had significantly:

- More parents who felt satisfied with the treatment [very low quality evidence]

There were no events of:

- Vomiting after discharge [low quality evidence]

HEAD to HEAD COMPARISON

Oral midazolam vs. oral triclofos sodium

Singh 2002[205]

- All patients in both groups completed the procedure [low quality evidence]

Compared with triclofos sodium group, the oral midazolam group had significantly:

- Shorted induction time [low quality evidence]
- Faster recovery time [low quality evidence]

Sublingual midazolam vs. oral chloral hydrate

Layangool 2008[136]

Compared to oral choral hydrate, the sublingual midazolam group had significantly:

- Shorter induction time [low quality evidence]
- Longer total time [low quality evidence]
- Less vomiting [low quality evidence]

There was no significant difference in:

- Completion of procedure [very low quality evidence]
- Duration of procedure [low quality evidence]

Enteral[#] midazolam vs. nitrous oxide (70%)

Zier 2008[239]

Based on the data provided, it was not possible to calculate the point estimate for the outcomes of parental satisfaction and total time.

Compared to nitrous oxide + placebo + topical anaesthesia + non-pharma intervention (distraction), the midazolam + placebo + topical anaesthesia + non-pharma intervention (distraction) group had significantly:

- More pain (FLACC); reported p=0.010 [moderate quality evidence]

There was no significant difference in:

- Vomiting during drug nitrous oxide administration [moderate quality evidence]

COMBINATION COMPARISONS

Oral midazolam vs. oral midazolam + nitrous oxide/oxygen

Al-zahrani 2009[13]

- All patients completed the procedure [low quality evidence]

There was no significant difference in:

- Induction time [low quality evidence]
- Duration of procedure [very low quality evidence]

[#] Enteral refers to any gastrointestinal route

Oral midazolam + nitrous oxide vs. nitrous oxide + placebo

Luhman 2001[152]

- All patients completed the procedure [moderate quality evidence]

There were no events of:

- Aspiration [moderate quality evidence]
- Respiratory intervention [moderate quality evidence]

There was no significant difference in:

- Vomiting during visit (during procedure and after the last suture was placed) [low quality evidence]

Oral midazolam + IV propofol vs. IV propofol

Paspatis 2006[178]

Compared with intravenous propofol + lidocaine, the oral midazolam + intravenous propofol + lidocaine group had significantly:

- Slower recovery time [moderate quality evidence]

There was no significant difference in:

- Duration of procedure [low quality evidence]

IV midazolam + IV meperidine vs. placebo + IV meperidine

Fishbein 1997[67]

There was no significant difference in:

- Distress with major negative behaviours as assessed by an observer using the Observational Behaviour Rating Scale (OBRS) [moderate quality evidence]
- Duration of procedure [low quality evidence]

IV midazolam + IV propofol vs. IV propofol

Disma 2005[56]

- All patients completed the endoscopy procedure [moderate quality evidence]

There was no significant difference in:

- The duration of procedure [moderate quality evidence]
- The recovery time [low quality evidence]
- Assisted ventilation (bag-mask) [low quality evidence]
- Oxygen desaturation < 90% [low quality evidence]

IV midazolam + IV morphine vs. IV propofol + IV morphine + local anaesthesia

Havel 1999[91]

- All patients completed the procedure [low quality evidence]

Compared to children in the intravenous propofol group, children in the intravenous midazolam group had significantly:

- Slower recovery time [low quality evidence]
- Longer total time [low quality evidence]

There were no events of:

- Aspiration [low quality evidence]
- Assisted ventilation [low quality evidence]
- Endotracheal intubation [low quality evidence]

There was no significant difference in:

- Induction time [low quality evidence]
- Duration of procedure [low quality evidence]
- Pain (number of patients) [very low quality evidence]

IV midazolam + IV fentanyl (analgesic) vs. IV fentanyl (analgesic)

Antmen 2005[16]

- All patients completed the procedure [low quality evidence]

There were no events of:

- Oxygen desaturation < 90% [low quality evidence]
- Vomiting [low quality evidence]

There was no significant different in:

- Pain (CHEOPS) [very low quality evidence]
- Pain (VAS) [very low quality evidence]

IV midazolam + IV remifentanil (analgesic) IV remifentanil (analgesic)

Antmen 2005[16]

- All patients completed the procedure [low quality evidence]

There were no events of:

- Oxygen desaturation < 90% [low quality evidence]
- Vomiting

There was no significant different in:

- Pain (CHEOPS) [low quality evidence][very low quality evidence]
- Pain (VAS) [very low quality evidence]

IV midazolam + IV ketamine vs. IV ketamine + placebo

Sherwin 2000[203]; *Wathen 2000*[229]

- All patients completed the procedures [moderate quality evidence]

Compared with intravenous ketamine + placebo, the intravenous midazolam + intravenous ketamine group had significantly:

- Less vomiting* [low quality evidence]

*during visit and at home 12 hrs after discharge[229] and well into recovery[203]

There was no significant difference in:

- Assisted ventilation (bag mask) [low evidence quality]

There were no events of:

- Aspiration [moderate quality evidence]

Dilli 2008[55]

Compared with intravenous ketamine + placebo, the intravenous midazolam + intravenous ketamine group had significantly:

- Shorter induction time [very low quality evidence]
- More satisfied parents [low quality evidence]

There was no significant difference in:

- Recovery time [very low quality evidence]

Wathen 2000[229]

There was no significant difference in:

- Parents' satisfaction [moderate quality evidence]
- Duration of procedure* [low evidence quality]

*As stated in the study. It was not possible to calculate the point estimate for this outcome based on the information reported in the study.

There were no events of:

- Endotracheal intubation [moderate quality evidence]

Sherwin 2000[203]; *Wathen 2000*[229]; *Dilli 2008*[55]

Compared with intravenous ketamine + placebo, the intravenous midazolam + intravenous ketamine group had significantly:

- More oxygen desaturation < 90% [low quality evidence]

ROUTE OF ADMINISTRATION COMPARISONS

Oral midazolam vs. intranasal midazolam

Connors 1994[42]

- All patients completed the suturing procedure [moderate quality evidence]

Everitt 2002[60]

Compared with intranasal midazolam, the oral midazolam group had significantly:

- Lower distress scores (VAS) [very low quality evidence]

Connors 1994[42]*; Everitt 2002*[60]

There was no significant difference in:

- Total time from administration to recovery area/discharge criteria being met [very low quality evidence]

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

Hartgraves 1994[90]

There was no significant difference in:

- The completion of procedure [low quality evidence]
- Oxygen desaturation < 90% [very low quality evidence]

Lee-Kim 2004[138]

Compared with intranasal midazolam, the oral midazolam group had significantly:

- Longer induction time [moderate quality evidence]
- Longer total time [low quality evidence]

Intranasal midazolam vs. intramuscular midazolam

Shashikiran 2006[202]

Compared with intramuscular midazolam, the intranasal midazolam group had significantly:

- Shorter induction time [moderate quality evidence]
- Shorter recovery time [moderate quality evidence]

There were no events of:

- Vomiting in either sedation group [moderate quality evidence]

DOSE COMPARISONS

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

Fuks 1994[71]

- All patients completed the procedure [moderate quality evidence]

There were no events of:

- Vomiting [moderate quality evidence]

Fukuta 1994[72]

There were no events of:

- Assisted respiration during and post dental treatment [moderate quality evidence]
- Vomiting post dental procedure [moderate quality evidence]

There was no significant difference in:

- The completion of procedure [low quality evidence]
- The duration of procedure [low quality evidence]
- Oxygen desaturation <90% [very low quality evidence]
- Vomiting during dental procedure [very low quality evidence]

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

Kanegaye 2003[124]

There were no events of:

- Cardiorespiratory complications [moderate quality evidence]

There was no significant difference in:

- Parents' satisfaction [low quality evidence]
- Total time [low quality evidence]
- Recovery time [low quality evidence]

6.3.3.2 Non RCT safety (adverse events)

For the characteristics of studies and outcome data on midazolam refer to Table 26 and Table 27.

Two studies reported rates of aspiration: 0%[141,157*]

- Three studies reported rates of endotracheal intubation: 0%[157,180,184]
- Two studies reported rates of assisted ventilation: from 0.16% to 0.60%[157,180]
- Three studies reported rates of external cardiac massage: from 0%[157,198] to 0.02%[141*]
- Two studies reported rates of defibrillation: from 0%[198] to 0.04%[141*]
- Five studies reported rates for vomiting: from 0.55% to 5.4%[98,141,157,180,191*]).
- Three studies reported rates for oxygen desaturation <90%: from 0.60% to 4%[98,157,180]
- One study reported two case episodes of apnoea with fentanyl and etomidate which required reversal[197]

*Lightdale 2009[141]: reported adverse events were based on a total sample of 5045 patients who received treatment as follows:

- IV midazolam (N=1,059); IV fentanyl (N=762); Chloral hydrate (N=604); Ketamine (N=513); Meperidine (N=21); Pentobarbital (N=2959)
- 20% (1017/5045) had two drugs in combination

6.3.4 GDG discussion of the evidence for midazolam

In clinical practice the GDG felt that midazolam is the most common sedative drug used however there was agreement that midazolam was probably not an effective sedative drug on its own apart from achieving mildly sedative effects and anxiolysis. Midazolam can be combined with various drugs including fentanyl, ketamine, propofol or nitrous oxide and evidence was found for these combinations. Overall the GDG felt that midazolam is a useful sedation drug and, based upon the evidence reviewed, that it is best used in combination with other drugs chosen to suit the needs of the clinical situation.

The studies reviewed by the GDG had been conducted for a variety of different reasons. The data derived from the studies were based upon different routes of administration together with differing drug combinations and doses. The sample sizes were small and the quality of the data was judged to be low.

Concerning the route of administration the GDG noted that oral and intranasal routes achieved a similar effect. There was no evidence comparing intravenous (IV) administration to other routes. The GDG agreed that IV drug administration acts more quickly than oral administration and once IV access is established further doses require little further cooperation unlike further doses via the intranasal or oral routes. However gaining IV access may cause distress. Overall the GDG agreed that Midazolam administered by any route helped to calm children prior to minor procedures or before the administration of more potent sedative drugs for painful procedures.

The GDG acknowledged that the safety data derived from both RCT data and observational studies showed that midazolam used on its own has a good safety profile provided that doses are limited. The GDG were aware of cases of paradoxical excitement.

When considering midazolam in combination with other drugs the GDG noted that evidence was available for ketamine, opioids, nitrous oxide (N_20) and propofol.

In combination with ketamine the GDG felt that the evidence demonstrated no more of an effect than for ketamine alone.

The GDG agreed that the evidence suggested that midazolam in combination with either opioids or nitrous oxide was effective for painful procedures. However when midazolam is used in combination with propofol it does not seem to result in any additional improvement in efficacy and the GDG agreed that midazolam is not necessary when using propofol.

The GDG debated vomiting as a side effect result of drug administration. For the combination of midazolam with opioids observational data suggested that vomiting was increased by approximately 5% however the GDG felt that an antiemetic may be effective with this drug combination. No evidence was available to determine if antiemetics were effective with this drug combination. It was noted that vomiting seems to be significantly decreased when midazolam is combined with ketamine[203,229].

When midazolam is combined with either ketamine, opioids or nitrous oxide deep sedation can result and the harms of using a combined drug approach for achieving sedation in children should be weighed against benefits of relieving the pain of the procedure.

Combination sedation with ketamine, opioids or nitrous oxide all risk possible oxygen desaturation and the need for airway intervention. The GDG noted the small numbers when looking at the adverse event data for assisted ventilation resulting from midazolam used in combination with other sedative drugs. When combined with ketamine one case (out of 180 children) of assisted ventilation was noted, for opioids 2/391 and 2/1226[180] and for nitrous oxide one case out of 168 children resulted in assisted ventilation. The GDG noted that there was more desaturation with the of midazolam ketamine combination than with ketamine alone.

The general principle agreed by the GDG is that only sedation techniques commonly available in the NHS should be included in the economic analysis. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). Midazolam combined with fentanyl was felt to be a strategy commonly used in colonoscopy, and there is some evidence that it is effective and well tolerated. The GDG therefore agreed that this strategy should be included in the economic analysis. Details of the considerations of cost-effectiveness with respect to using this combination strategy in this population group are given in section 6.12.3.2.

The GDG also felt that the use of midazolam alone in dental procedures in adolescents and in oesophago-gastroscopy is common, and there is some evidence on the effectiveness and safety of using midazolam alone. The GDG agreed that an economic analysis should be done on the use of midazolam alone in dental procedures in adolescents, and in children undergoing oesophago-gastroscopy. The details of the considerations of the cost-effectiveness for using this strategy in the two population groups are given in sections 6.12.4.2. and 6.12.3.2 respectively.

6.4 Ketamine

Matrix of ketamine comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Isoflurane = I
Ketamine=K
Local anaesthesia = LA
Midazolam = M
Nitrous oxide = N_20
Nitrous oxide and oxygen = N_20+02
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Ketamine vs			
	Reference	**Tables**	**Evidence statements page**
Placebo			
Nil			
Head to head			
Nil			
Combinations			
K + M vs M + F	Kennedy 1998[129] Lucas Da Silva 2007[151] Tosun 2007[215]	Table 28 Table 29	210
K + M vs M	Acworth 2001[10]	Table 30	211
K + P vs P + F	Tosun 2007[215]	Table 31	211
K + M vs P + F	Godambe 2003[77]	Table 32	212
K + M vs regional block	Kriwanek 2006[132]	Table 33	212
K + M vs N_20+haematoma block	Luhmann 2006[153]	Table 34	212
P + F + K vs P + F	Erden 2009[59]	Table 35	213

Safety			
RCTs			
Desaturation	Kennedy 1998[129] Lucas Da Silva 2007[151] Acworth 2001[10] Tosun 2007[215] Godambe 2003[77] Erden 2009[59] Roback 2006[192]	Table 37 Table 38	213
Vomiting	Kennedy 1998[129] Acworth 2001[10] Tosun 2007[215] Godambe 2003[77] Luhmann 2006[153] Roback 2006[192]	Table 37 Table 38	213
Observational studies	McGlone 2004[163] Sacchetti 2007[197] Roback 2005[191] Green 1998[82] Green 1998[81] Green 2001[80] Gilger 2004 McQueen 2009[164] Ramaswamy 2009[188] Thorp 2009[214] Treston 2009[218]	Table 37 Table 38	213
Route of administration			
IV / IM	Roback 2006[192]	Table 36	213
Dose			
Nil			

6.4.1 Clinical methodological introduction for ketamine

CLINICAL QUESTIONS:

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?

- safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy and safety of ketamine. The search was expanded to include non RCT observational studies for the safety of ketamine.

There were no systematic reviews identified for the use of ketamine in paediatric sedation.

There were no placebo controlled studies identified.

Nine RCTs comparing IV/IM ketamine with other sedative drugs and with regional anaesthesia were assessed for efficacy.

Seven RCTs met the inclusion criteria for the review of the safety of ketamine.

Meta-analysis was not performed as there were no studies in which comparisons and outcome measures were sufficiently homogenous to calculate a meaningful summary statistic.

Eleven non RCT observational studies assessed the safety of ketamine in a total of 6892 patients.

6.4.2 Evidence profiles for ketamine

6.4.2.1 RCT evidence profiles for efficacy and safety for ketamine

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

DRUG COMBINATION COMPARISONS

Table 28: Ketamine/midazolam vs. midazolam/fentanyl; Kennedy 1998[129]

Author(s): Kennedy 1998[129]
Question: Should ketamine/midazolam IV vs. fentanyl/midazolam be used for pediatric orthopedic emergencies?
Settings: A & E

Quality assessment							Summary of findings						Importance
							No of patients		Effect		Quality		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine/midazolam IV	Fentanyl/Midazolam	Relative (95% CI)	Absolute			
Completion of procedure (follow-up mean 121 minutes)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	129/130 (99.2%)	127/130 (97.7%) 0%	RR 1.02 (0.95 to 1.02)	20 more per 1000 (from -49 fewer to 20 more) 0 more per 1,000	LOW		
Distress score - assessed by observer: VALIDATED scales (follow-up mean not stated minutes; measured with: OSBD-R score; range of scores: 0-23.5; Better indicated by less)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3,4]	none	130	130	-	MD -1.62 (-2.04 to -1.2)	LOW		
Pain score- assessed by parent: VALIDATED scales (follow-up Not stated minutes; measured with: 10 point VAS; higher scores indicate greater pain; range of scores: 0-10; Better indicated by less)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3,5]	none	130	130	-	MD 1.34 (-2.15 to -0.53)	LOW		
Anxiety score - assessed by parent: VALIDATED scales (follow-up Not stated minutes; measured with: 10 point VAS; higher scores indicate greater anxiety; range of scores: 0-10; Better indicated by less)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3,5]	none	130	130	-	MD -1.01 (-1.8 to -0.22)	LOW		
Induction time -Time in minutes between first midazolam dose and first orthopedic manipulation (follow-up mean 13 minutes; measured with: minutes; range of scores: Better indicated by less)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	130	130	-	MD -0.30 (-3.1 to 2.5)	LOW		
Total time: time from administration of intervention to when patient has been transferred to the recovery area (follow-up mean 120 minutes; measured with: minutes; range of scores: Better indicated by less)													
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	130	130	-	MD 13.90 (2.34 to 25.46)	LOW		
Adverse event: oxygen saturation <90% (follow-up throughout sedation minutes; Pulse oximetry)													
1	randomised	serious[1,2]	no serious	no serious	serious[3]	none	8/130 (6.2%)	31/130 (23.8%)	RR 0.26	176 fewer per			

	trial		inconsistency	indirectness					(0.11 to 0.55)	1000 (from 107 fewer to -212 fewer)	LOW	
Adverse event: vomiting during sedation and recovery (follow-up during sedation and recovery minutes)												
1	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/130 (6.9%)	2/130 (1.5%)	RR 4.51 (1.01 to 17)	53 more per 1000 (from 0 more to 240 more)	LOW	

[1] The study was quasi randomised. Subjects were stratified according to initial parental choice to remain in the room or not during reduction. Subjects were then randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine. A random number generator used.
[2] The study was not fully blinded. Two trained observers were blinded to study purpose and design reviewed the videotape of each study. Unable to blind sedators. Blinding of patients and parents was not described.
[3] Small sample size
[4] OBSD-R may be biased by subjectivity of observer
[5] Parental observations may be subjective and therefore biased

Table 29: Ketamine/midazolam vs. fentanyl/midazolam; Lucas Da Silva 2007[151]

Author(s): Lucas Da Silva 2007[151]
Question: Should ketamine/midazolam IV vs. fentanyl/midazolam be used for procedural sedation for insertion of CV catheter?
Settings: In hospital CV catheter insertion

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Midazolam/ketamine IV	Midazolam/fentanyl	Relative (95% CI)	Absolute		
Completion of procedure (follow-up mean 101 minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/29 (100%)	28/28 (100%)	RR 1 (0 to 0)	0 fewer per 1000 (from 1000 fewer to 1000 fewer)	LOW	
								0%		0 fewer per 1,000		
Recovery time: Time elapsed from end of procedure to awakening (follow-up median 20 minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	-5.0 (-15 to 7.9)	LOW	
Total time: Time elapsed from initial sedative administration to spontaneous eye opening (follow-up median 101 minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	6.5 (-19 to 33)	LOW	
Induction time: Time elapsed from initial sedative administration to onset of the procedure (follow-up median 7.5 minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	2 (-0.002 to 5.998)	LOW	
Adverse event: oxygen saturation <90% (follow-up median 101 minutes; Pulse oximeter)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/29 (6.9%)	0/28 (0%)	RR 4.83 (0.24, 96.42)	0 more per 1000 (from 0 fewer to 0 more)	LOW	

[1] Double blinding was deemed impractical because of different dosing algorithms of the drugs used and because medications used present clinically distinguishable effects.
[2] Small sample size
[3] Recovery time, induction time and total times were reported as median differences

Table 30: Ketamine + midazolam vs. intranasal midazolam; Acworth 2001[10]

Author(s): Acworth 2001[10]
Question: Should intravenous ketamine plus midazolam vs. intranasal midazolam be used for emergency paediatric procedural sedation?
Settings: A & E

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV ketamine plus midazolam	intranasal midazolam	Relative (95% CI)	Absolute		
Completion of procedure (follow-up mean 88 minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious	none	26/26 (100%)	26/26 (100%) 0%	RR 1.07 (0.81 to 1.08)	70 more per 1000 (from -190 fewer to 80 more) 0 more per 1,000	LOW	
Induction time (time from administration of sedation until sedation score reached 3 or less) (follow-up mean 5 minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	MD 5.32 (3.2 to 7.4)	LOW	
Total time: timing - total: time from administration of intervention to when patient met all the criteria for discharge (follow-up mean 88 minutes; measured with: minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	MD -18.9 (-33.4 to -4.4)	LOW	
Adverse events: oxygen saturation <09% (follow-up mean 88 months)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/26 (3.8%)	0/26 (0%)	RR 3.12 (0.12 to 80.12)	0 more per 1000 (from -0 fewer to 0 more)	LOW	
Adverse event: vomiting during procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/26 (0%)	1/26 (3.8%)	RR 0.33 (0.01 to 6.46)	25 fewer per 1000 (from 38 fewer to 207 more)	LOW	

[1] Drug route precluded double blinding and allocation concealment but the doctor and nurse responsible for scoring sedation level were not present during drug administration and were blinded to allocation by use of dummy armboard applied to children receiving the intranasal medication
[2] The sample size was only 26 in each group

Table 31: Ketamine + propofol vs. propofol + fentanyl; Tosun 2007[215]

Author(s): Tosun 2007[215]
Question: Should intravenous ketamine plus propofol vs. propofol plus intravenous fentanyl be used in children undergoing upper GI endoscopy?
Settings: Gastroenterology

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ketamine IV plus propofol	propofol plus fentanyl IV	Relative (95% CI)	Absolute		
Completion of procedure (follow-up mean 116 minutes (time to discharge))												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/46 (100%)	44/44 (100%)	RR 1 (0 to 0)	0 fewer per 1000 (from 1000 fewer to 1000 fewer)	MODERATE	
Pain (Number of patients who needed additional propofol during induction as evidenced by discomfort/moving during procedure (follow-up 0-1 minute after induction)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/46 (17.4%)	22/44 (50%)	RR 0.35 (0.17 to 0.7)	325 fewer per 1000 (from 150 fewer to 415 fewer)	LOW	
Pain (Number of patients who needed additional propofol during as evidenced by discomfort/moving during procedure)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32/46 (69.6%)	41/44 (93.2%)	RR 0.75 (0.61 to 0.92)	233 fewer per 1000 (from 75 fewer to 363 fewer)	LOW	
Recovery time (time from completion of procedure to recovery/discharge criteria being met) (follow-up mean 4.5 minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	44	-	MD 1.60 (-0.42 to 3.62)	LOW	
Adverse events: oxygen saturation <90% (follow-up mean 116 minutes; Pulse oximetry)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/46 (6.5%)	4/44 (9.1%) 25%	RR 0.75 (0.16 to 2.83)	23 fewer per 1000 (from 76 fewer to 167 more) 62 fewer per 1,000	LOW	
Adverse events: vomiting (follow-up mean 116 minutes; observation)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/46 (15.2%)	0/44 (0%)	RR 16.9 (0.93 to 305.47)	0 more per 1000 (from -0 fewer to 0 more)	LOW	

[1] Unclear allocation concealment; small trial, total n=90; no loss to follow up; double blind
[2] Wide confidence interval; few events

Table 32: Ketamine/midazolam vs. propofol/fentanyl; Godambe 2003[77]

Author(s): Godambe 2003[77]
Question: Should ketamine/midazolam vs. Propofol/Fentanyl be used for Procedural Sedation ?
Settings: Pediatric Emergency Department

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine/Midazolam	Propofol/Fentanyl	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/54 (92.6%)	53/59 (89.8%)	RR 1.03 (0.86 to 1.09)	27 more per 1000 (from -126 fewer to 81 more)	LOW	
Recovery time: last dose of medication to return to baseline (follow-up time to return to baseline minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	59	-	MD 33.4 (26.1 to 40.8)	LOW	
Total time; from first dose of medication to return to baseline (follow-up Total time from beginning of sedation to recovery minutes; measured with: minutes; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	59	-	MD 23.2 (15.4 to 30.4)	LOW	
Adverse events: vomiting (follow-up Immediate adverse effects minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/54 (3.7%)	0/59 (0%)	RR 5.67 (0.27 to 120.73)	0 more per 1000 (from -0 fewer to 0 more)	LOW	
Adverse outcome: oxygen saturation <90% (follow-up Any amount of time during procedure and recovery minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/54 (7.4%)	18/59 (30.5%)	RR 0.24 (0.08 to 0.67)	232 fewer per 1000 (from 101 fewer to -281 fewer)	LOW	
Pain score - assessed by parent: VALIDATED scales (measured with: VAS score; range of scores: 0mm-100mm; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	30	38	-	MD 4.30 (-5.28 to 13.88)	LOW	
Distress score- assessed by observer - VALIDATED scales (follow-up Video tapes /OSBD score assessed after procedure minutes; range of scores: 0-23.5; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	54	59	-	MD -0.19 (-0.39 to 0)	LOW	

[1] Quasi randomised - Odd or even day assignment
[2] Small sample size

[3] Assessment by parents may be subjective and therefore biased
[4] There is potential for the OSBD to be subjective and therefore biased

Table 33: Ketamine/midazolam vs. axillary block regional anesthesia (intra arterial block); Kriwanek 2006[132]

Author(s): Kriwanek 2006[132]
Question: Should ketamine plus midazolam vs. axillary (brachial plexus) block regional anesthesia be used for forearm fracture in children?
Settings: Pediatric Emergency Department

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine + midazolam	Axillary (brachial plexus) block regional anesthesia(ABRA)	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/21 (100%)	18/20 (90%)	RR 1.09 (0.78 to 1.11)	81 more per 1000 (from -198 fewer to 99 more)	LOW	
Pain -score - assessed by patient: VALIDATED scales (measured with: FPS-R ; range not provided; range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	21	20	-	MD 0.90 (-0.27 to 2.07)	LOW	
Pain -score - assessed by observer: VALIDATED scales (measured with: CHEOPS during fracture reduction; range of scores: 4-13; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	21	20	-	MD 1.10 (-0.31 to 2.51)		

[1] Blinding not possible and allocation concealment not described.
[2] Small sample size
[3] Pain scales have potential for subjective interpretation and therefore bias

Table 34: Ketamine + midazolam vs. nitrous oxide + haematoma block; Luhmann 2006[153]

Author(s): Luhmann 2006[153]
Question: Should ketamine plus midazolam vs. nitrous oxide plus haematoma block be used for forearm fracture reduction in children?
Settings: Emergency Department

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine +Midazolam	Nitrous Oxide + Hematoma Block	Relative (95% CI)	Absolute		
Completion of procedure (follow-up mean 50 minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55/55 (100%)	47/47 (100%)	RR 1 (0 to 0)	0 fewer per 1000 (from 1000 fewer to 1000 fewer) 0 fewer per 1,000	LOW	
Adverse event: vomiting (follow-up mean 50 months)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/55 (23.6%)	12/47 (25.5%) 0%	RR 0.92 (0.44 to 1.7)	20 fewer per 1000 (from 143 fewer to 179 more) 0 fewer per 1,000	LOW	
Recovery time (follow-up mean 49.5 minutes; measured with: P value reported for mean difference of 83 minutes for KM group and 16 minutes for NO/HB group: p<0.0001; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55	47	-	MD 0 (0 to 0)	LOW	
Distress during procedure (measured with: OR of MD reported: OR 0.9 (95% CI 0.5-2.1); range of scores: 5-25; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	55	47	-	MD 0 (0 to 0)	LOW	
Pain - reported by patient (follow-up mean 49.5 minutes; measured with: OR of mean difference in VAS scores reported: OR 1.1 (95% CI 0.0-2.1); range of scores: 1-10; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	55	47	-	MD 0 (0 to 0)	LOW	
Pain - reported by parent during procedure (follow-up mean 49.5 minutes; measured with: OR of mean difference in VAS scores reported: OR 1.6 (95% CI 0.6-2.6); range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,5]	none	55	47	-	MD 0 (0 to 0)	LOW	

[1] Single blinding only
[2] Small sample size
[3] Distress scale has potential for subjectivity and therefore bias
[4] Pain as assessed by patient is inherently subjective and therefore subject to bias
[5] Pain as assessed by parent is inherently subjective and therefore subject to bias

Table 35: Ketamine + Propofol-fentanyl vs. propofol-fentanyl; Erden 2009[59]

Author(s): Erden 2009[59]
Question: Should ketamine plus propofol-fentanyl vs. propofol-fentanyl be used in paediatric sedation?
Settings: Interventional radiology

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ketamine + propofol-fentanyl	propofol-fentanyl	Relative (95% CI)	Absolute		
Oxygen saturation <90%												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	3/30 (10%)	9/30 (30%)	RR 0.33 (0.10 to 1.11)	201 fewer per 1000 (from 270 fewer to 33 more) 0 fewer per 1,000	MODERATE	

[1] Sample size small and characterised as 'about' 30 patients for each group would be sufficient to detect a fall from 30% to 5%

ROUTE OF ADMINISTRATION COMPARISONS

Table 36: Intravenous ketamine vs. intramuscular ketamine; Roback 2006[192]

Author(s): Roback 2006[192]
Question: Should intravenous ketamine vs. intramuscular ketamine be used for sedation of pediatric patients?
Settings: Emergency Department Orthopedic Procedures

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV ketamine	IM ketamine	Relative (95% CI)	Absolute		
Completion of procedure (follow-up median 13.0 minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	101/109 (92.7%)	95/99 (96%)	RR 0.97 (0.82 to 1.02)	29 fewer per 1000 (from 173 fewer to 19 more)	LOW	
Adverse events: oxygen saturation <90% (Pulse oximetry)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/109 (8.3%)	4/99 (4%)	RR 2.05 (0.65 to 5.75)	42 more per 1000 (from -14 fewer to 190 more)	LOW	
Adverse event: vomiting												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/109 (11.9%)	26/99 (26.3%)	RR 0.39 (0.23 to 0.84)	160 fewer per 1000 (from 42 fewer to -203 fewer)	LOW	
Pain score - number of patients - assessed by patient: VALIDATED scales												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	49/84 (58.3%)	57/70 (81.4%)	RR 0.72 (0.49 to 0.92)	228 fewer per 1000 (from 65 fewer to -415 fewer)	LOW	
Distress - score - assessed by observer during procedure: VALIDATED scales (range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	97	93	-	MD 0.47 (0.13 to 0.82)	LOW	
Timing - total: time from administration of intervention to when patient has been transferred to the recovery area (follow-up median 104.5 minutes; measured with: Reported as range: 27-210 minutes IV; 55-365 minutes IM; p<.001; range of scores: 27-365; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	109	99	-	0 (0 to 0)	LOW	

[1] Single blinding only
[2] Small sample size
[3] The FACES scale is a subjective measurement and is subject to bias
[4] OBSD scale has potential to be subjective and therefore biased

6.4.2.2Non RCT evidence profiles for safety for ketamine

Eleven non RCT observational studies in 6892 patients assessed the safety of ketamine[76,80-82,163,164,188,191,197,214,218]. There were six prospective reviews and five retrospective studies conducted primarily for emergency procedures (9) as well as studies of ketamine for gastrointestinal (GI) procedures.

The non RCT study characteristics for ketamine are presented in Table 37.

The non RCT adverse event table for ketamine is presented in Table 38.

1 **Table 37: Ketamine Non RCT study characteristics safety review**

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Prospective Cohort						
McGlone et al, 2004[163] UK	Lancaster Royal Infirmary, Lancaster, UK Accident and emergency department		IM ketamine sedation for minor painful procedures		IM ketamine: 301 children received 2.0 mg/kg and 191 received 2.5 mg/kg; 26 children received a second dose.	
Sacchetti et al, 2007[197] USA Results from ProSCED Registry for Ketamine	14 community emergency departments	321 (94.1%) were ASA I, 18 were ASA class II (5.3%) and 2 were ASA class III (0.6%)	41.3% received ketamine – route of delivery not described			
McQueen et al, 2009[164]	A children's hospital emergency department, USA		66% (363) received ketamine alone; 19% (106) received ketamine/midazolam; 15% (85) received non-ketamine drugs	62% (341) were male; 38% (213) were female		

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Ramaswamy et al, 2008[188]	Royal Children's Hospital Melbourne, Australia ED		Ketamine IM or IV	138 male (60.3%)	Ketamine 3-4 mg/kg IM or 1-1.5 mg/kg IV	
Thorp et al, 2009[214]	Pediatric Emergency Department, Loma Linda University Medical Center and Children's Hospital, Loma Linda, California USA	ASA I 93% (959); ASA II 6% (66); ASA III 1% (14)	Ketamine	62% (649) male	Ketamine initial dose (0.2-2.4 mg/kg) and total dose (0.3 to 23.8 mg/kg)	
Treston et al, 2009[218]	Redcliffe Hospital Brisbane, Australia		Ketamine for minor procedures or		Ketamine from 0.23 to 3.8 mg/kg (mean 1.15	

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
	ED		examination		mg/kg). Titrated IV ketamine used in 691 cases and IM in 54 cases	
Roback et al, 2005[191] USA	Paediatric Emergency Department		IV or IM procedural sedation		Ketamine alone; ketamine/midazolam	
Green et al, 1998[82] USA	Emergency Department		IM Ketamine		Ketamine 4 mg/kg combined with atropine .01mg/kg IM; repeat ketamine dose (2-4 mg/kg) without atropine if required	Children who had eaten a full meal within 3 hours were excluded but not those with lesser degrees of oral intake
Green et al, 1998[81] USA	Emergency Department		IV Ketamine		The mean loading dose of ketamine was 1.5 + 0.5 mg/kg and was then titrated as necessary. The total mean dose used was 2.5 + 1.6 mg/kg.	Children who had eaten a full meal within 3 hours were excluded but not those with lesser degrees of oral intake
Green et al, 2001[80] USA	University medical centre - Department of Gastroenterology	Ketamine administered at all levels of ASA stratification	IV Ketamine: 98.3% of patients and IM Ketamine: 1.7% of patients Concurrent midazolam was administered in 97% (614) of patients	54.4%	The median IV loading dose of ketamine was 1.00 mg/kg and titrated if necessary. The median total IV dose was 1.34 mg/kg.	

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Gilger et al, 2004[76] USA	Children's Hospital: endoscopy		Ketamine + midazolam; Ketamine + midazolam + meperidine	48% male in ketamine/midazolam group; 63% male in the Ketamine + midazolam + meperidine group	Ketamine 0.75-2.0 mg/kg dose	

Table 38: Ketamine Safety: Non RCTs

Study type, reference, country	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)									GRADE PROFILE
					Aspiration	Respiratory intervention			Cardiac arrest requiring either/or		vomiting	oxygen desaturation <90%	Recovery agitation	Evidence quality
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation				
Prospective Cohort studies														
McGlone et al, 2004[163] UK	IM Ketamine	Injuries in A&E requiring wound toilet and suturing, minor surgery such as nail bed repair, and removal of foreign bodies	Not stated	501							17% (in recovery or at home) (85/501)	.5% (3/501))	Mild: 15% (71/501) Moderate: 3% 16/501 Pronounced: 0.8% (4/501)	VERY LOW
Sacchetti et al, 2007[197] USA Results from ProSCED Registry for Ketamine	Ketamine	Minor trauma including laceration repairs, foreign body removal, fracture care, join relocation and also lumbar puncture, radiology, tube thoracostomy and cardioversion	Ages 0-20 years	This registry reports a total of 1028 procedural sedations. 141 children received ketamine										VERY LOW
McQueen et	Ketamine	Emergency	3 months	422							25/422			VERY

Study type, reference,	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)									GRADE PROFILE
al, 2009[164]		Department procedures	-18 years								(5.9%) Before discharge			LOW
	Ketamine/ midazolam			123							13/123 (10.5%) before discharge			VERY LOW
Ramaswamy et al, 2008[188]	IM Ketamine vs. IV ketamine	Emergency Department procedures	1.8-4.3 years	229 total; IM, n= 110; IV, n= 119 .							IM: 17.3% (95% CI = 10.7% to 25.7%) vs. IV: 11.8% (95% CI = 6.6% to 18.9%); P=0.24	IM: 4.5% (95% CI= 1.5% to 10.3%) vs. IV 4.2%, (95% CI= 1.4% to 9.5%); p=0.9		VERY LOW
Thorp et al, 2009[214]	Ketamine	Emergency Department procedures	No emesis: 6.1 years median age; With emesis 9.8 years median age	1039							Rate of emesis was 7.0% when the total dose was 7 mg/kg or less and 11.1% when greater than 7 mg/kg			VERY LOW
Treston et al, 2009[218]	Ketamine	Emergency Department procedures	12 months – 13 years	745									16/745 (2,1%)	VERY LOW
Retrospective														
Roback et al, 2005[191]	Ketamine	Fracture reduction;	39 days to 22	1,492								6.1% 91/1492		VERY LOW

Study type, reference,	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)									GRADE PROFILE
USA		laceration repair; lumbar puncture; imaging; other dental	years; median age 6.58 years									Includes oxygen saturation >90% and laryngospasm		
	Ketamine/midazolam		4.8 mo to 18 y; median age 6.21 years	299								10%30/299 Includes oxygen saturation >90% and laryngospasm		VERY LOW
Green et al, 1998[82] USA	IM Ketamine	Emergency procedures including wound and dermal repair, orthopaedic, GU, GI eye procedures and line placement, lumbar puncture, CT scan chest tube and ET tube placement	0-15 years	1,022				.4% (5/1022) Bag mask ventilation			6.7% (68/1022)	.9% (9/1022)	Total events by chart documentation and assessed by physician: 19.3% (197/1022) Moderate to severe: 1.6% (16/1022)	VERY LOW
Green et al, 1998[81] USA	IV Ketamine 31% received	Emergency procedures including	0-15 years	156				.6% (1/156) Bag mask			3.8% (6/156) 1 while	.6% (1/156)	Total events by chart	VERY LOW

Study type, reference,	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)									GRADE PROFILE
	concurrent midazolam	wound and dermal repair, orthopaedic, GU, GI eye procedures and line placement, lumbar puncture, CT scan chest tube and ET tube placement						ventilation			sedated and 5 in recovery		documentation: Mild:1.3% (2/156) Moderate to severe: 0	
Green et al, 2001[80] USA	IV Ketamine: 98.3% of patients and IM Ketamine: 1.7% of patients Concurrent midazolam was administered in 97% (614) of patients 15% of patients received other sedatives: meperidine (n=90), diazepam (n=4) and morphine	GI procedures	Median age 5.2 years	636 46% of patients had severe underlying illness (ASA >3)				3% (19/636) Bag mask ventilation			4.1% (26/636)		1.4% (9/636) mild .9% Moderate to severe	VERY LOW

Study type, reference,	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)									GRADE PROFILE
	(n=3)													
Gilger et al, 2004[76] USA	Ketamine + midazolam	GI endoscopy	5.9 years mean age (SD 4.77)	128	0						0	*data recorded was oxygen saturation <95%	0	VERY LOW
	Ketamine + midazolam + meperidine		7.68 years mean age (SD 4.22)	82				1.2% (1/82)			0	*data recorded was oxygen saturation <95%	0	VERY LOW

IV= intravenous; IN= intranasal; IM= intramuscular; INH= inhaled

6.4.3 Evidence statements for ketamine

6.4.3.1 RCT efficacy and safety for ketamine

DRUG COMBINATION COMPARISONS

Ketamine/midazolam vs. fentanyl/midazolam

Kennedy 1998[129]

Compared with midazolam + fentanyl, the midazolam + ketamine group had significantly:

- Less distress on Observation Scale of Behavioral Distress (OSBD) [low quality evidence]
- Less anxiety as reported by parent on Visual Analogue Scale (VAS) after procedure [low quality evidence]
- Less pain as reported by parent on VAS after procedure [low quality evidence]
- Longer total time [low quality evidence]
- Less oxygen desaturation (O_2 saturation <90%) [low quality evidence]
- More vomiting during recovery; p=.03 [low quality evidence]

There was no significant difference in:

- Completion of procedure [low quality evidence]
- Length of induction [low quality evidence]

Ketamine/midazolam vs. fentanyl/midazolam

Lucas Da Silva 2007[151]

Median results were reported on this RCT. It was not possible to combine these results with other studies for meta-analysis.

Compared with midazolam + fentanyl, the midazolam + ketamine group had significantly:

- Shorter induction time [low quality evidence]

There was no significant difference in:

- Completion of procedure – all procedures were completed [low quality evidence]
- Recovery time [low quality evidence]

- Total sedation time [low quality evidence]
- Oxygen saturation <90% [low quality evidence]

It was stated that neither cardiac rhythm abnormalities nor increase in cardiac rate were detected.

Ketamine + midazolam + vs. intranasal midazolam

Acworth 2001[10]

Compared with midazolam + ketamine, the intranasal midazolam group had significantly:

- Shorter induction time [low quality evidence]
- Longer total time [low quality evidence]

There was no significant difference in:

- Completion of procedure – all procedures were completed [low quality evidence]
- Oxygen saturation <90% [low quality evidence]
- Vomiting [low quality evidence]

Ketamine-propofol vs. fentanyl-propofol

Tosun 2007[215]

- All patients completed the procedure [Moderate quality evidence]

Compared with Propofol-fentanyl, the propofol-ketamine group had significantly:

- Less pain as measured by the number of patients requiring additional propofol in the first minute after induction [low quality evidence]
- More vomiting [Low quality evidence]

There was no significant difference in:

- Recovery time [low quality evidence]
- Oxygen saturation <90% [low quality evidence]

Ketamine + midazolam vs. propofol + fentanyl

Godambe 2003[77]

Compared with propofol + fentanyl, the midazolam + ketamine group had significantly:

- Less oxygen desaturation (O_2 saturation <90%) [low quality evidence]
- More vomiting during recovery [low quality evidence]
- Longer total time [low quality evidence]

There was no significant difference in:

- Completion of procedure – all procedures were completed [low quality evidence]
- Length of induction [low quality evidence]
- Less distress on OSBD (Observational Scale of Behavioural Distress) [low quality evidence]
- Less pain as reported by parent on VAS after procedure [low quality evidence]

Ketamine + midazolam vs. axillary block regional anaesthesia

Kriwanek 2006[132]

There was no significant difference in:

- Completion of procedure – all procedures were completed [low quality evidence]
- Pain assessed by patient using FPS-R [low quality evidence]
- Distress during the procedure as measured by CHEOPS scale¸[low quality evidence]

Ketamine + midazolam vs. nitrous oxide + haematoma block

Luhmann 2006[153]

Compared with nitrous oxide + haematoma block, the ketamine + midazolam group had significantly:

- Longer recovery time (from cast moulding to Aldrete score of 10) [low quality evidence]

There was no significant difference in:

- Completion of procedure – all procedures were completed [low quality evidence]
- Distress as assessed by PBCL score [low quality evidence]

- Pain assessed by patient using VAS [low quality evidence]
- Pain assessed by parent using VAS [low quality evidence]
- Vomiting [low quality evidence]

Propofol-fentanyl vs. propofol-fentanyl-ketamine

Erden 2009[59]

Compared with Propofol-fentanyl, the propofol-fentanyl-ketamine group required significantly:

- Less supplemental propofol [moderate quality evidence]

There was no significant difference in:

- Oxygen saturation <90% [moderate quality evidence]

ROUTE OF ADMINISTRATION COMPARISONS

Intravenous ketamine vs. intramuscular ketamine

Roback 2006[192]

Compared with ketamine IM, the ketamine IV group had significantly:

- Less distress during the procedure as measured by CHEOPS scale [low quality evidence]
- Less total time [low quality evidence]
- Less vomiting [low quality evidence]

There was no significant difference in:

- Completion of procedure [low quality evidence]
- Oxygen saturation <90% [low quality evidence]
- Pain assessed by patient using FPS-R [low quality evidence]
- Parental satisfaction assessed on 7 point Likert scale [low quality evidence]

6.4.3.2NON-RCT safety (adverse events)

For the characteristics of studies and outcome data on ketamine refer to Table 37 and Table 38.

- Four studies reported rates of assisted ventilation: 1.2%[76] ; 0.6%[82]; 0.4%[81]; 3%[80]

- There were no cardiac events reported in 11 studies.

- Vomiting was reported in nine studies[76,80-82,163,164,188,214,218]. and rates ranged from 0%[76], to17%[163]. The mean vomiting rate for the nine studies was 7.9%. A dose response effect was noted in one study[214] where the rate of emesis was 7.0% when the total dose was 7 mg/kg or less and 11.1% when greater than 7 mg/kg. A non significant difference was noted between IV and IM routes[188].

- Oxygen saturation <90% was reported in five studies[81,82,131,163,188,191]. and rates ranged from 0.5%[163] to 10%[191]. The mean desaturation rate for five studies was 3.8%.

- Recovery agitation was reported in seven studies and was classified as mild, moderate and severe. Definitions of these classifications were not standardised. Mild recovery agitation ranged from 1.3[81], -15%[163]; moderate to severe recovery agitation ranged from 0%[81], to 1.6%[81].

6.4.4 GDG discussion of the evidence for ketamine

The GDG noted that out of 16 studies considered 11 were in patients undergoing painful procedures in the Emergency Department (ED) setting. One study was in children undergoing painful insertion of central intravenous catheters and the remainder were in children undergoing gastrointestinal endoscopy.

The GDG discussed four studies[82,163,192,197] in which ketamine was used alone in the ED setting. Only one of these studies[192] was an RCT and it compared IV with IM ketamine. The quality of the evidence was low yet, together with the three large non-RCTs[82,163,197], the GDG agreed that there was much evidence to show that ketamine was effective over a wide range of painful procedures.

Discussions highlighted the difficulty of research in this area. The main problem was that any sedation technique being compared with ketamine would need to be of a similar efficacy. That there were so few studies may indicate that few sedation techniques are as effective as ketamine. The GDG thought that combinations of drugs such as midazolam and fentanyl were potentially as effective.

In the RCT comparing intravenous versus intramuscular ketamine[192] the GDG noted that the evidence of efficacy was limited to the successful outcome of the procedure. There were no data about the level of sedation achieved. The GDG agreed that the level of sedation achieved by ketamine alone was dependent on dose but that the sedation level was often uncertain because ketamine induces a sedated state in which the patient is not responsive but has their eyes open. In this state, known as dissociative sedation, vital reflexes remain intact to maintain breathing and prevent aspiration. The GDG discussed whether or not some of the patients were anaesthetised rather than sedated and it was appreciated that high doses could cause anaesthesia in which vital reflexes may be obtunded. It was agreed that it was not possible to be certain about what dose was compatible with sedation rather than anaesthesia.

Evidence showed that intravenous and intramuscular administrations were equally effective for painful procedures in the emergency department setting and the GDG discussed the advantages and disadvantages of both methods. Intravenous administration facilitates the titration of smaller doses of ketamine and therefore reduces the chance of sedation outlasting the intended procedure. The GDG agreed that intramuscular is a painful route of administration and should be reserved for situations when intravenous administration is impractical. However it was noted that despite local anaesthesia skin preparation intravenous cannulation may be painful and attempts may need to be repeated if initially unsuccessful. Consequently it may be reasonable to offer a single intramuscular injection rather than wait for local anaesthesia to be applied to the skin and become effective in a child in whom venous access may prove to be difficult.

The GDG considered the evidence for ketamine combined with other drugs. There were five RCTs[10,77,129,151,215] in which a combination of ketamine and midazolam had been compared with other drugs. All were low quality evidence. In four studies[77,129,132,153] the authors stated that the target level of sedation was deep. The main efficacy outcome was completion of procedure and all procedures were completed in these RCTs. In comparison with a midazolam fentanyl combination the ketamine midazolam combination was associated with lower pain and distress scores. In comparison with propofol and fentanyl combination the ketamine midazolam combination was also associated with lower pain and distress scores although the recovery time was longer. In both comparisons ketamine midazolam combinations were associated with less oxygen desaturations. The GDG agreed that this was likely to be for two reasons. First, it may be more difficult to titrate a combination of midazolam and fentanyl than ketamine and midazolam; second, fentanyl causes more respiratory depression than ketamine.

Two studies[132,153] compared the ketamine midazolam combination with techniques involving local anaesthesia for reduction of forearm fractures; the local anaesthesia was supplemented by midazolam alone in one and nitrous oxide in the other, and all techniques seemed equally effective.

The GDG discussed the problems of designing a RCT to determine the effect of combining ketamine with other drugs. For example in order to determine the effect of combining ketamine with midazolam it would be necessary to have a comparator group receiving midazolam alone. This however would not be possible because midazolam alone would not be effective for painful procedures. If a ketamine was compared with a ketamine midazolam combination the results would indicate the effect of midazolam. Nevertheless, if it was assumed that ketamine was effective it would be reasonable to consider such a study as evidence of how ketamine alone compared with the combination. The GDG reconsidered two RCTs[203,229] that compared ketamine alone with ketamine combined with midazolam that had already been reviewed in the midazolam evidence to recommendation discussions. It was agreed that the addition of midazolam conferred no significant advantage and was associated with more oxygen desaturation.

The GDG discussion focused on airway and breathing effects of ketamine. In some studies 10-15% of children had oxygen desaturation after ketamine but the GDG recognised that these events were usually brief and easily managed with oxygen and simple airway support. The level of desaturation may have been related to the skills of the healthcare practitioner. Nevertheless, evidence showed that potentially dangerous airway effects could occur after ketamine by either route. The need for the use of “bag and mask ventilation" was estimated to be approximately 1-2% but was less than this in some large cohort studies. Laryngospasm was the usual cause of airway obstruction although apnoea is known to be a potential hazard also. The GDG agreed that airway management skills and equipment are essential for this drug.

The GDG discussed the three studies[76,80,215] of ketamine combined with various drugs for endoscopy procedures. A study comparing the ketamine midazolam combination with a propofol fentanyl combination showed that ketamine was associated with more laryngospasm during gastroscopy. The GDG considered that ketamine causes more salivation than propofol and that the combination of pharyngeal secretions during gastroscopy[215] is likely to lead to laryngospasm.

The problem of fasting before ketamine was also discussed in the emergency department setting. It was agreed that the fasting status of a child in the emergency setting is often uncertain and that the stomach emptying is often delayed after trauma. The GDG felt that in the emergency setting, when sedation is required for an emergency procedure, there was a good trade-off between the benefit of prompt sedation with ketamine and the hazard of vomiting and aspiration. The GDG agreed that ketamine has a safe reputation for use in children who may not be fasted although the quality of evidence for risk of aspiration was very low. In order to prove that ketamine was well tolerated in unfasted children, it was recognised that large numbers of children would need to be studied, some of whom were fasted and others not fasted, before this safety question could be answered with confidence.

Other side effects were also discussed. Vomiting was a common minor side effect but there was no evidence to show that any intervention prevented it. The GDG agreed that there should be research into methods of reducing vomiting with ketamine. Emergence phenomena including hallucinations are a recognised complication of the use of ketamine; the GDG noted that these are uncommon and not reduced by routine administration of midazolam, although if distressing can be effectively treated with intravenous midazolam.

Discussions led to how ketamine sedation compared with anaesthesia in the setting of a painful procedure in an emergency department. The GDG could find no evidence to confirm which approach is best but GDG members knew that the issue has been debated recently in the Emergency Medicine professional journals. It was agreed that there were potential economic advantages to providing sedation within a few hours of admission rather than waiting for the services of an anaesthesia team that may involve overnight admission. The GDG recognised that this was a common dilemma. However in many hospitals emergency department staff are currently not trained to administer ketamine. Training of a team to deliver ketamine sedation was considered to be essential if ketamine was to be used safely.

The agreement by the GDG is that economic analysis should be conducted only for sedation techniques commonly available in the NHS. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). The GDG felt there is some evidence that ketamine alone is effective and well tolerated. It is commonly used in short painful procedure in the NHS, and it was therefore agreed that this strategy should be compared to other relevant strategies in the economic analysis conducted for this population group. Details of the considerations of cost-effectiveness with respect to using ketamine alone in short painful procedures are given in section 6.12.1.2.

6.5 Chloral hydrate

Matrix of chloral hydrate comparators			
Key: Chloral hydrate = CH Fentanyl = F Isoflurane = I Ketamine=K Local anaesthesia = LA Midazolam = M Nitrous oxide = $N_2 0$ Nitrous oxide and oxygen = $N_2 0+02$ Opioids = O Propofol= P Sevoflurane = S Triclofos sodium = TS			
Chloral hydrate vs			
	Reference	**Tables**	**Evidence statements page**
Placebo			
	Houpt 1989[96]	Table 39	233
Head to head			
M	Dallman 2001[49]	Table 40	233
General Anaesthetic (GA)	Thompson 1982[213]	Table 41	233
Music	Loewy 2005[150]	Table 42	233
Combinations			
CH + hydroxyzine vs M + acetaminophen	Dallman 2001[49] Reeves, 1996[189]	Table 43	234
Safety			
RCTs	Marti-Bonmati 1995[159]	Table 45	234
Vomiting	Houpt 1989[96]	Table 46 Table 48	235

Observational studies	Ronchera-Oms 1994[194] Napoli 1996[171] Greenberg 1991[83] Greenberg 1993[84] Malviya 2000[156] Fox 1990[69] Heistein 2006[92] Cortellazzi 2007[43] Needleman 1995[173]	Table 46 Table 48	235
Route of administration			
Nil			
Dose			
CH high dose vs CH low dose	Houpt 1985[97]	Table 44	233
CH intermediate dose vs CH high dose	Marti-Bonmati 1995[159]	Table 45	234

6.5.1 Clinical methodological introduction for chloral hydrate

CLINICAL QUESTIONS:

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?

The literature was searched for systematic reviews and RCTs for the clinical efficacy and safety of chloral hydrate. The search was expanded to include observational studies for the safety of chloral hydrate.

No systematic reviews were identified for the use of chloral hydrate in paediatric sedation.

Seven RCTs met the inclusion criteria for the review of the efficacy of chloral hydrate.

Two RCTs met the inclusion criteria for the review of the safety of chloral hydrate.

Meta-analysis was not performed as there were no studies in which comparisons and outcome measures were sufficiently homogenous to calculate a meaningful summary statistic.

Nine non RCTs assessed the safety of chloral hydrate in a total of 5,188 patients.

6.5.2 Evidence profiles for chloral hydrate

6.5.2.1 RCT evidence profiles for efficacy and safety for chloral hydrate

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

PLACEBO COMPARISONS

Table 39: Chloral hydrate vs. placebo; Houpt 1989[96]

Author(s): Houpt 1989[96]
Question: Should chloral hydrate vs. placebo be used in children also receiving nitrous oxide?
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chloral Hydrate	Placebo	Relative (95% CI)	Absolute		
Vomiting												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/19 (10.5%)	1/19 (5.3%)	RR 2.00 (0.2 to 20.24)	53 more per 1000 (from 42 fewer to 1000 more)	LOW	

[1] Small sample size and wide confidence levels for relative effect
[2] Generation code and allocation concealment not described

HEAD TO HEAD COMPARISONS

Table 40: Chloral hydrate vs. intranasal midazolam; Dallman 2001[49]

Author(s): Dallman 2001[49]
Question: Should chloral hydrate vs. intranasal midazolam be used for paediatric sedation?
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chloral hydrate	intranasal midazolam	Relative (95% CI)	Absolute		
Recovery Time												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/31 (77.4%)	30/31 (96.8%)	RR 49.00 (3.11 to 771.67)	1000 more per 1000 (from 1000 more to 1000 more)	LOW	

Table 41: Chloral hydrate vs. general anaesthesia; Thompson 1982 [213]

Author(s): Thompson 1982[213]
Question: Should chloral hydrate vs. GA be used in paediatric sedation?
Settings: CT

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chloral hydrate	GA	Relative (95% CI)	Absolute		
Complete procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/101 (84.2%)	101/101 (100%) 0%	RR 0.84 (0.77 to 0.92)	160 fewer per 1000 (from 80 fewer to 230 fewer) 0 fewer per 1,000	LOW	
Induction time (range of scores: 25-55; Better indicated by less)												
1	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101	101	[3]	MD 30[3]	LOW	
Duration of procedure (range of scores: 48-80; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101	101	[4]	MD 32[4]	LOW	

[1] Inadequate randomisation, allocation concealment. No blinding. Distribution of ages not equal: 203 infants 0-1month, 82 children ages 1-2 years and remaining equally divided between years 2-0 years.
[2] No explanation was provided
[3]~Reported mean per group: 55 minutes vs. 25 minutes
[4]Reported mean per group: 48 minutes vs. 80 minutes

Table 42: Chloral hydrate vs. music therapy; Lowey 2005[150]

Author(s): Loewy 2005[150]
Question: Should chloral hydrate vs. music therapy be used in paediatric sedation?
Settings: EEG

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chloral hydrate	music therapy	Relative (95% CI)	Absolute		
Complete procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/24 (50%)	33/34 (97.1%)	RR 0.52 (0.34 to 0.77)	466 fewer per 1000 (from 223 more to 1000 fewer)	LOW	
Induction time(measured with: minutes; range of scores: 23-32; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	33	[3]	MD 9.0[3]	LOW	
Total time (measured with: minutes; range of scores: 66-226; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	33	[4]	MD 160[4]	LOW	

[1] Generation code and allocation concealment not described. Study was unblinded.
[2] Small sample size
[3] Reported mean per group: 23 minutes vs. 32 minutes
[4] Reported p<0.001; mean per group: 66 minutes vs. 226 minutes

COMBINATION COMPARISONS

Table 43: Chloral hydrate/hydroxyzine vs. midazolam/acetaminophen; Reeves 1996[49,189]

Author(s): Reeves, 1996[189]
Question: Should chloral hydrate/hydroxyzine vs. midazolam/acetaminophen be used in paediatric sedation?
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chloral hydrate/hydroxyzine	Midazolam /acetaminophen	Relative (95% CI)	Absolute		
Distress by Houpt score (range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD -0.10 (-0.83 to 0.63)		

[1] Generation code and allocation concealment not described
[2] Small sample size. Assessment has elements of subjectivity.

DOSE COMPARISONS

Table 44: High dose vs. low dose chloral hydrate; Houpt 1985[97]

Author(s): Houpt 1985[97]
Question: Should High dose chloral hydrate vs. Low dose chloral hydrate be used for sedation in children?
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	High dose chloral hydrate	Low dose chloral hydrate	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/17 (76.5%)	16/17 (94.1%) 0%	RR 0.81 (0.61 to 1.09)	179 fewer per 1000 (from 367 fewer to 85 more) 0 fewer per 1,000	LOW	
Induction time (measured with: minutes; range of scores: 9-24; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	MD 15 (0 to 0)	LOW	

[1] Randomisation and allocation concealment not described.
[2] Small sample size (<20 patients per group)

Table 45: Intermediate dose chloral hydrate vs. high dose chloral hydrate; Marti-Bonmati 1995[159]

Author(s): Marti-Bonmati et al, 1995[159]
Question: Should intermediate dose chloral hydrate vs. high dose chloral hydrate be used for sedation in children?
Settings: MRI

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intermediate dose chloral hydrate	High dose chloral hydrate	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/50 (92%)	47/47 (100%)	RR 0.92 (0.84 to 1.01)	80 fewer per 1000 (from 160 fewer to 10 more)	MODERATE	
Length of induction time (measured with: minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	47	-	MD 7 (6.38 to 7.62)	MODERATE	
Recovery time (measured with: minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	47	-	MD -8.00 (-10.2 to -5.8)	MODERATE	
All adverse events												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/50 (20%)	10/47 (21.3%)	RR 0.94 (0.43 to 2.05)	13 fewer per 1000 (from 121 fewer to 224 more)	MODERATE	

[1] Method of randomisation and allocation concealment not adequately described.

6.5.2.2Non RCT safety(adverse events) for chloral hydrate

Nine non RCT observational studies with greater than 300 subjects (total n= 5,188) assessed the safety of chloral hydrate[194]. There were six prospective reviews and three retrospective studies conducted primarily for imaging procedures (7) as well as one dental and one ophthalmic study.

The non RCT study characteristics for chloral hydrate are presented in Table 46.

The non RCT adverse event data for chloral hydrate is presented in Table 48.

1 **Table 46: Chloral hydrate Non RCT study characteristics safety review**

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Prospective Cohort						
Ronchera-Oms et al[194] Spain	MRI	Not stated	Chloral hydrate for imaging	55% male	Chloral hydrate syrup 70 mg/ml	Permitted oral fluids before examination
Napoli et al[171] USA	Echocardiography	Not stated	Chloral hydrate for imaging	Not stated	Median dose of chloral hydrate was 77 mg/kg	Not stated
Greenberg et al[83] USA	CT	Not stated	Chloral hydrate for imaging	63% male	100 mg/kg in a single dose with maximum of 2 grams	Not stated
Greenberg et al[84] USA	MRI	Not stated	Chloral hydrate for imaging	Not stated	100 mg/kg	Not stated

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Malviya et al[156] USA	MRI	72% ASA I; 27% ASA II and 1% as ASA III.	Sedation to facilitate outpatient diagnostic imaging procedures	53% male	64 ± 13 mg/kg chloral hydrate	Not stated
Fox et al[69] USA	Ophthalmic examination	Not stated	Chloral hydrate for ophthalmic procedures in infants and young children	Not stated	80-100 mg/kg chloral hydrate not to exceed 3 g.	NPO for 4 hours prior to administration of chloral hydrate
Retrospective Studies					100 mg/kg chloral hydrate	
Heistein et al[92] USA*	Echocardiography	7.3% ASA 1; 54.4% ASA II; 37.4% ASA III and 0.8% ASA IV	Chloral hydrate sedation for echocardiography	Not stated	Oral chloral hydrate (80 mg/kg, maximum 1 g)	Infants less than 6 months could receive formula and solids for up to 6 hours, breast milk for up to 4 hours and clear liquids for up to hours before sedation. Children 6 months or older could receive solids and liquids for up to 6 hours and clear liquids for up to 2 hours before sedation
Cortellazzi[43] Italy	MRI	Not stated	Level 3 on Skeie Scale – asleep but easily aroused	61% male	50 – 100 mg/kg to a maximum dose of 1.5 g/kg	Determined according to the ASA recommendations

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Needleman et al[173] USA	Dental	ASA I or I	Conscious sedation	56% male	Average dose of chloral hydrate 776 mg (55 mg/kg)	'Pre-operative dietary restrictions'

*In this study potential risk factors were assessed for their association with adverse events. Univariate analysis identified age younger than 6 months, cyanotic heart disease and hospitalization at the time of the study as significant risk factors. Multivariate analysis identified only age younger than 6 months as a significant independent risk factor for the occurrence of an adverse event.

Table 47: Chloral hydrate safety: RCTs and Non RCTs (n = >300 patients)

Study type, reference, country	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)								GRADE PROFILE
					Aspiration	Respiratory intervention			Cardiac arrest requiring either/or		vomiting	oxygen saturation <90%	EVIDENCE QUALITY
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
Prospective Cohort studies													
Ronchera-Oms et al[194] Spain	Chloral hydrate	MRI	Mean age 41 ± 30 months	596							6.9% (41)	0	VERY LOW
Napoli et al[171] USA	Chloral hydrate	Echocardiography	3 weeks to 14 years; median age 13 months	405							6% (23)	6% (24) defined as greater than 5% drop from baseline in these children with heart disease	VERY LOW
Greenberg et al[83] USA	Chloral Hydrate: high dose of 80-100 mg/kg	CT	Mean age 2.18 years	326	1 aspiration of secretions by child with severe mental retardation		2 due to obstruction of the airway by the tongue. One child was profoundly retarded.				4.3% (14)		VERY LOW
Greenberg et al[84] USA	Chloral hydrate	MRI	1 month – 11 years	300							4% (12)		VERY LOW
Malviya et al[156] USA	Chloral hydrate	MRI/CT	3.8 ± 3.4 years	336							3% (8) has 'GI effects' in hospital; 26% (78) had 'GI' effects at home		VERY LOW
Fox et al[69]	Chloral hydrate	Ophthalmic exam-	1 month - 5	302							0	0	VERY LOW

Study type, reference, country	**Drug / Comparison**	**Procedure**	**Age**	**Total N**	**ADVERSE EVENTS, rate: % (n)**								**GRADE PROFILE**
					Aspiration	Respiratory intervention			Cardiac arrest requiring either/or		vomiting	oxygen saturation <90%	**EVIDENCE QUALITY**
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
USA		ination	years										
Retrospective Studies													
Heistein et al[92] USA*	Chloral hydrate	Echocardiography	Birth to 64 months	1095 38% were ASA 3 or 4; 88% had detectable heart disease; 78% received a single agent and 22% received >1 medication	0	0.3% (3) required oral or nasal suctioning	0.1% (1) required intubation	0.1% (1) required bag-mask ventilation			0.4% (4)	5.9% (65) defined as greater than 10% drop from baseline in these children with heart disease	VERY LOW
Cortellazzi et al[43] Italy	Chloral hydrate	MRI	Mean age 28.2 ± 18.1 months	888 procedures using chloral hydrate alone for MRI in neurologically impaired children			0	0			0.2% (n=2)	0.5% (n=4)	VERY LOW
Needleman et al[169] USA	Chloral hydrate	Dental	Mean age 2.6 years	336							8.1%(27)		VERY LOW

*In this study potential risk factors were assessed for their association with adverse events. Univariate analysis identified age younger than 6 months, cyanotic heart disease and hospitalization at the time of the study as significant risk factors. Multivariate analysis identified only age younger than 6 months as a significant independent risk factor for the occurrence of an adverse event.

6.5.3 Evidence statements for chloral hydrate

6.5.3.1 RCT efficacy and safety for chloral hydrate

PLACEBO COMPARISONS

Chloral hydrate vs. placebo

Houpt 1989[96]

No efficacy outcomes of interest were reported in this study. One adverse event outcome of interest was reported in this study.

There was no significant difference in:

- Number of children who vomited [low quality evidence]

HEAD TO HEAD COMPARISONS

Chloral hydrate vs. intranasal midazolam

Dallman 2001[49]

Compared to intranasal midazolam, the chloral hydrate group had significantly:

- Longer recovery time [low quality evidence]

Chloral hydrate vs. GA

Thompson 1982[213]

Compared to GA, the chloral hydrate group had significantly:

- Fewer completed procedures [low quality evidence]
- Longer induction time [low quality evidence]
- Shorter procedure time; [low quality evidence]

Chloral hydrate vs. music therapy

Loewy 2005[150]

Compared to music therapy, the chloral hydrate group had significantly:

- Fewer completed procedures [low quality evidence]
- Longer total time asleep [low quality evidence]

There was no significant difference in:

- Induction time [low quality evidence]

COMBINED COMPARISONS

Chloral hydrate + hydroxyzine vs. midazolam + acetaminophen

Reeves 1996[49,189]

There was no significant difference in:

- Distress scores [low quality evidence]

DOSE COMPARISONS

High dose vs. low dose chloral hydrate

Houpt 1985[97]

Compared to low dose chloral hydrate (mean 708 mg), the high dose chloral hydrate (mean 1062 mg) group had significantly:

- Fewer procedure failures [low quality evidence]
- Shorter induction time [low quality evidence]

Intermediate dose chloral hydrate vs. high dose chloral hydrate

Marti-Bonmati 1995[159]

In this study, sedation was judged a failure if the MRI imaging study could not be completed, if additional sedation other than chloral hydrate was required for completion of the study or if fewer than 95% of the images were acceptable.

Compared to intermediate dose chloral hydrate (70 mg/kg), the high dose chloral hydrate (96 mg/kg) group had significantly:

- Less induction time [moderate quality evidence]

There was no significant difference in:

- Completion of MRI [moderate quality evidence]
- Recovery time [moderate quality evidence]

- Total adverse events (events were not reported individually) [moderate quality evidence]

6.5.3.2NON-RCT safety (adverse events) for chloral hydrate

For the characteristics of studies and outcome data on chloral hydrate refer to Table 46and Table 48.

- One prospective study[83] of high dose chloral hydrate reported 1 aspiration of secretions by child with severe mental retardation and 2 endotracheal intubations due to obstruction of the airway by the tongue. One child was profoundly retarded.

- One retrospective study[92] reported that 0.3% of children receiving chloral hydrate required oral or nasal suctioning, 0.1% required intubation and 0.1% required bag-mask ventilation.

- No respiratory events were reported in seven studies.

- No cardiac events were reported in nine studies.

- The mean vomiting rate for 9 non RCT observational studies of chloral hydrate was 4.1%[43,69,83,84,92,156,171,173,194]. One study[156] reported that 26% (78) of patients had 'GI' effects at home.

- One study[171] reported oxygen saturation drop greater than 5% from baseline in 6% of patients.

- One study[92] reported oxygen saturation drop greater than 10% from baseline in 5.9% of patients.

- One study[43] reported 0.5% rate of oxygen saturation <90%.

6.5.4 GDG discussion of the evidence for chloral hydrate

Chloral hydrate is an oral drug and unfortunately causes nausea and vomiting when large volumes of the drug are used. The GDG agreed that chloral hydrate is therefore likely to be less successful in larger children. Some GDG members thought more than 1g of chloral hydrate may be vomited and hence be unsuccessful. This may explain why choral is thought to be more effective in smaller children.

The GDG considered 14 studies[43,49,69,83,84,92,97,150,156,159,171,189,194,213] of chloral hydrate used alone; two others[96,173] were of chloral hydrate combined with other drugs. Ten of these studies were in children undergoing painless procedures; five for dental treatment[49,96,97,173,189] and one for ophthalmic examination[69]. Of the painless procedure studies, five were for MRI[43,84,156,159,194] and two for CT imaging[83,213].

Two RCTs[159,213] were found for painless imaging. One study[159] showed that high dose chloral hydrate was not more effective than low dose for MRI but that high dose chloral hydrate caused shorter onset of sedation (the evidence level was moderate). The other study[213] showed that anaesthesia was more effective than chloral hydrate for CT imaging (the evidence level was low). The other studies were non-RCT.

The GDG concluded that uncooperative children needed to be asleep for imaging and that high doses of chloral hydrate were successful in approximately 90% of children under 15kg. High doses were likely to be more reliable than low doses.

The GDG debated as to what sedation level was achieved by chloral hydrate in the painless imaging setting. The GDG noted that the doses of chloral hydrate used caused the children to sleep and, because the success of the scanning required them to be immobile and undisturbed, the true sedation level achieved was uncertain. The GDG members appreciated that all children in the evidence studies were likely to be either moderately or deeply sedated. Nevertheless the GDG agreed that unconsciousness was possible and that appreciable airway and breathing effects could be caused in a small percentage of children. These problems were uncommon but were reported. In one cohort study[83] a child with severe mental retardation suffered pulmonary aspiration during sedation.

The disadvantages of chloral hydrate are that it is administered as a single oral dose, that it cannot therefore be titrated, and that its effect is variable in terms of depth of sedation, and its onset and recovery times. However there are potential economic advantages of chloral hydrate if its success rate is high enough because anaesthesia resources may be saved (both techniques are equally safe).

There was evidence of chloral hydrate being used in other settings. Chloral hydrate combined with nitrous oxide was shown in one study[96] to be more effective than nitrous oxide alone in young children having dental treatment. This combination however was associated with vomiting in 10% of cases.

Chloral hydrate was also useful for calming small irritable children for echocardiography and in this setting the GDG appreciated that anaesthesia would not usually be appropriate.[92,171]

The GDG noted that small children could be sedated successfully with chloral hydrate for eye examination. In another study[150] the GDG noted that children could be calmed for EEG studies more effectively by music rather than chloral hydrate however the GDG thought that this was an unusual setting and that children having EEG are not required to be immobile

The GDG agreed that economic analysis should be conducted only for sedation techniques commonly available in the NHS. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). Chloral hydrate was felt to be effective and safe. It is commonly used in painless imaging in the NHS. The GDG therefore agreed that this strategy should be included in the economic analysis conducted for patients undergoing painless imaging. Details of the considerations of cost-effectiveness with respect to using chloral hydrate in painless imaging are given in section 6.12.2.2.

6.6 Triclofos sodium

Matrix of triclofos sodium comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Isoflurane = I
Ketamine=K
Local anaesthesia = LA
Midazolam = M
Nitrous oxide = N_20
Nitrous oxide and oxygen = N_20+02
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Triclofos sodium vs			
	Reference	**Tables**	**Evidence statements page**
Placebo			
Nil			
Head to head			
TS vs M	Singh 2002[205]	Table 48	240
Combinations			
Nil			
Safety			
RCTs	-		
Observational studies	Nil		
Route of administration			
Nil			
Dose			
Nil			

6.6.1 Clinical methodological introduction for triclofos sodium

CLINICAL QUESTIONS:

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?

- Safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews RCTs for the clinical efficacy of triclofos sodium. The search was expanded to include non RCT observational studies for the safety of triclofos sodium.

There were no systematic reviews identified for the use of triclofos sodium in paediatric sedation.

One RCT was found that compared triclofos sodium with midazolam. Whilst efficacy data was reported safety data was not. There were no non-RCT observational studies assessing the safety of triclofos sodium.

Meta-analyses were not performed as there was only one RCT.

6.6.2 Evidence profiles

6.6.2.1 RCT evidence profiles for efficacy and safety

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

HEAD to HEAD COMPARISONS

Table 48: Oral triclofos sodium vs. oral midazolam; Singh 2002[205]

Question: Should oral triclofos sodium vs. oral midazolam be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: Dental
Bibliography: Singh 2002[205]

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral triclofos sodium	oral midazolam	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/30 (100%)[2]	30/30 (100%)	not estimable	-	LOW	
Induction time (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 16.10 (14.09 to 18.11)3	LOW	
Recovery time: when the patient was able to sit or stand alone with minimal assistance (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 38.23 (31.52 to 44.94)3	LOW	

[1] Singh 2002[205]: patients and outcome assessors blinded however concealment, ITT and attrition details not stated; small study
[2] Singh 2002[205]: ease of treatment completion rated as 1-excellent, 2-difficult and 3-impossible; study stated that treatment was most convenient for midazolam group than for triclofos group. Difficulty in treatment was significantly more for the group of promethazine than for midazolam (p<0.01) and for triclofos (p<0.05)
[3] Singh 2002[205]: p<0.00001

6.6.2.2 Non RCT evidence profiles for safety for triclofos sodium

There were no non RCT observational studies of triclofos sodium.

6.6.3 Evidence statements for triclofos sodium

RCT efficacy and safety *for triclofos sodium*

HEAD to HEAD COMPARISONS

Oral triclofos sodium vs. oral midazolam

Singh 2002[205]

- All patients completed the procedure [low quality evidence]

Compared with the oral midazolam group, the oral triclofos sodium group had significantly:

- Longer induction time [low quality evidence]
- Slower recovery time [low quality evidence]

Non RCT safety (adverse events) *for triclofos sodium*

There were no non RCT observational studies of triclofos sodium.

6.6.4 GDG discussion of the evidence for triclofos sodium

Only one study[205] of triclofos was found and it compared triclofos with midazolam for dental procedures. The GDG noted that triclofos was not effective in this setting and also that the quality of evidence was very low.

The GDG noted that the properties of triclofos and chloral hydrate were similar and that triclofos may cause less gastric irritation. The GDG discussed the potential advantages of triclofos but without evidence this drug could not be recommended as more effective than chloral hydrate.

The GDG felt that triclofos sodium is not among the sedation drugs commonly used in the NHS, and decided that it should not be included in the economic analysis.

1 ## 6.7 Nitrous Oxide

Matrix of nitrous oxide comparators			
Key: Chloral hydrate = CH Fentanyl = F Isoflurane = I Ketamine=K Local anaesthesia = LA Midazolam = M Nitrous oxide = N_20 Nitrous oxide and oxygen = N_20+02 Opioids = O Propofol= P Sevoflurane = S Triclofos sodium = TS			
Nitrous oxide vs			
	Reference	**Tables**	**Evidence statements page**
Placebo			
N_20 vs Oxygen	McCann 1996[161] Primosch 1999[187]	Table 49 Table 50	258 258
N_20 vs nitrogen and oxygen	Fauroux 2004[64]	Table 51	**Error! Bookmark not defined.**
Head to head			
N_20 vs Behavioural management	Veerkamp 1993[224] Veerkamp 1995[222]	Table 52	258
N_20 vs Midazolam	Wilson 2007[235] Wilson 2003[231] Wilson 2006[232] Wilson 2002[233] Wilson 2002[234]	Table 53 Table 54 Table 55	259 259 259
N_20 + EMLA vs EMLA	Ekbom 2005[58]	Table 56	260
Combinations			
N_20 + M vs air + M	Averley 2004[20]	Table 57	260
N_20 + M vs S + N_20 + M	Averley 2004[20]	Table 58	261
N_20 + M + S vs air +	Averley 2004[20]	Table 59	261

M			
Safety			
RCTs			
Desaturation	Primosch 1999[187]	Table 60 Table 61	261
Observational studies	Babl 2008[21] Gall 2001[73] Faddy 2005[61]	Table 60 Table 61	261
Route of administration			
Nil			
Dose			
Nil			

6.7.1 Clinical methodological introduction for nitrous oxide

CLINICAL QUESTIONS:

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?

- safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy and safety of nitrous oxide. The search was expanded to include observational studies for the safety of nitrous oxide.

No systematic reviews were identified for the use of nitrous oxide in paediatric sedation.

There were no placebo controlled trials identified.

Twelve RCTs met the inclusion criteria for the review of the efficacy of nitrous oxide.

Four RCTs met the inclusion criteria for the review of the safety of nitrous oxide.

Three non RCTs assessed the safety of nitrous oxide in a total of 8,220 patients.

Meta-analysis were performed if comparisons and outcome measures were sufficiently homogenous to calculate a meaningful summary statistic[222,224,232-234].

6.7.2 Evidence profiles for nitrous oxide

6.7.2.1 RCT evidence profiles for efficacy and safety for nitrous oxide

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

PLACEBO COMPARISONS

Table 49: Nitrous oxide vs. oxygen; McCann 1996[161]

Author(s): McCann 1996[161]
Question: 50% nitrous oxide vs. 100% oxygen for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	50% nitrous oxide	100% oxygen	Relative (95% CI)	Absolute		
Quiet behaviour on OSUBRS												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/20 (95%)	15/20 (75%)	RR 1.27 (0.96 to 1.66)	202 more per 1,000	LOW	

[1] Randomisation and allocation concealment not described

Table 50: Nitrous oxide vs. oxygen; Primosch 1999[187]

Author(s): Primosch 1999[187]
Question: 40% nitrous oxide vs. 100% oxygen for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	40% nitrous oxide	100% oxygen	Relative (95% CI)	Absolute		
Quiet behaviour on OSUBRS (measured with: OSBU ordinal scale; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious	none	22	22	[3]	not pooled[3]	LOW	
Oxygen saturation (range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22[4]	22	[4]	MD 0.00 (-0.01 to 0.01) [4]	LOW	

[1] Randomisation and allocation concealment not described.
[2] Small sample size.
[3] RR behaviour scores not estimable due to use of an ordinal scale and incomplete statistical information; reported scores: 713 for N2O group and 630 for O2 group; reported $p<0.001$.
[4] Values in the two groups were exactly the same, 99+ 0.01.

Table 51: Nitrous oxide vs. nitrogen and oxygen; Fauroux 2004[64]

Author(s): Fauroux 2004[64]
Question: 50% nitrous oxide vs. 50% nitrogen & oxygen for sedation in children
Settings: Broncoscopy

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	50% nitrous oxide	50% nitrogen & oxygen	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/53 (20.8%)	32/52 (61.5%)	RR 0.34 (0.19 to 0.6)	406 fewer per 1000 (from 246 fewer to 498 fewer)	LOW	
								61.5%		405 fewer per 1,000		
Pain score: CHEOPS (range of scores; better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53	53	-	MD -1.3 (-2.09 to -0.51)	LOW	
Pain: VAS for children >6 years (range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	13	-	MD -28 (-34.44 to -21.56)	LOW	

[1] Randomisation and allocation concealment not described.
[2] Small sample size not adequate to achieve power calculation of 90%

HEAD TO HEAD COMPARISONS

Table 52: Nitrous oxide vs. behavioural management; Veerkamp 1993[224]; Veerkamp 1995[222]

Author(s): Veerkamp 1993[224]; Veerkamp 1995[222]
Question: Nitrous oxide vs. behavioural management for sedation in children
Setting: Dental

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	nitrous oxide	behavioural management	Relative (95% CI)	Absolute		
Anxiety (range of scores: -; Better indicated by less)												
2	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	51	-	MD -0.54 (-0.88 to -0.2)	VERY LOW	

[1] Randomisation method and allocation concealment not described. There was only partial blinding
[2] Two studies by same investigator with small sample sizes

Table 53: Nitrous oxide vs. transmucosal midazolam; Wilson 2007[235]

Author(s): Wilson 2007[235]
Question: Nitrous oxide vs. transmucosal (buccal) midazolam for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrous oxide	transmucosal (buccal) midazolam	Relative (95% CI)	Absolute		
Length of induction (range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	36	-	not pooled[3]	LOW	
Duration of procedure (range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	36	-	not pooled[4]	LOW	
Total time (range of scores: Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	36	-	not pooled[5]	LOW	
Patient preference												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/36 (55.6%)	10/36 (27.8%)	RR 2 (1.1 to 3.65)	277 more per 1,000	LOW	

[1] Single blind trial
[2] Small sample size. 80% power calculation required 40 subjects. Only 36 patients completed the study and were analysed.
[3] Unable to calculate as SD not given: 7.1 mean minutes vs. 14.4 mean minutes; reported p <0.001
[4] Unable to calculate as SD not given: 8.0 mean minutes vs. 10.1 mean minutes; reported p <0.001.
[5] Unable to calculate as SD not given: 34.1 mean minutes vs. 64.7 mean minutes; reported p <0.001.

Table 54: Nitrous oxide vs. intravenous midazolam; Wilson 2003[231]

Author(s): Wilson 2003[231]
Question: Should IV midazolam vs. nitrous oxide be used for paediatric sedation?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV midazolam	nitrous oxide	Relative (95% CI)	Absolute		
Duration of procedure (measured with: measured with median minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	not pooled[3]	LOW	
Length of induction (measured with: measured with median minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	not pooled[4]	LOW	
Total time (measured with: median minutes; range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	MD 34.4 (36.42 to 32.38)	LOW	
Patient preference - number of patients												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/37 (51.4%)	14/37 (0%)	RR 1.36 (0.81 to 2.28)	0 more per 1,000	LOW	
Recovery time (range of scores: -; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	MD 28.3 (26.10 to 30.80)	LOW	

[1] Unable to blind
[2] Small sample size
[3] Results given as median times thus absolute effect could not be estimated; reported p<0.01
[4] Results given as median times thus absolute effect could not be estimated; reported p<0.001

Table 55: Nitrous oxide vs. oral midazolam; Wilson 2006; Wilson 2002; Wilson 2002[232-234]

Author(s): Wilson 2002, BDJ[234] Wilson 2002 Anaesthesia[235] Wilson 2006 Anaesthesia[232]
Question: 30% nitrous oxide/70% oxygen vs. oral midazolam for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	30% nitrous oxide/70% oxygen	oral midazolam	Relative (95% CI)	Absolute		
Induction time (range of scores: Better indicated by less)												
2	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	61	-	not pooled[3]	MODERATE	
Recovery time (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	not pooled[4]	MODERATE	
Duration of procedure (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	61	-	not pooled[5]	MODERATE	
Total time (range of scores: Better indicated by less)												
2	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	61	-	not pooled[6]	MODERATE	
Patient preference (Questionnaire)												
2	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/72 (54.2%)	41/73 (56.5%)	RR 0.97 (0.72 to 1.29)	16 fewer per 1,000	MODERATE	

[1] These were all randomised crossover trials. Trial data is combined where possible for 1-3 studies.
[2] Small sample size
[3] Two studies[232,234] reported mean (range) times and mean differences were not estimable; reported p<0.001 and p<0.0001 respectively. Another study[233] reported induction times as median values , 5 [5-10] minutes for N2O compared to 20 [5-65] minutes for oral midazolam; reported p<0.001
[4] Two studies[232,234]: reported mean (range) times in Wilson 2002 and thus mean differences were not estimable; reported 20 minutes for N2O and 39.7 minutes for midazolam; p<0.0005. Wilson 2002[233] reported median times: 5 [5-10] minutes for N2O compared to 20 [5-65] minutes for oral midazolam; p<0.001
[5] Studies were not able to be combined to provide a summary statistic due to differences in data reporting and missing data[232,234]
[6] Two studies[232,234] reported mean (range) times and mean differences were not estimable; reported p<0.001 and p<0.0005 respectively. Another study[233] reported total time as median values , 35 [30-50] minutes for N2O compared to 100 [70-140] minutes for oral midazolam, p<0.001

Table 56: Nitrous oxide + EMLA vs. EMLA; Ekbom 2005[58]

Author(s): Ekbom 2005[58]
Question: Should Nitrous oxide + EMLA vs. EMLA be used for intravenous cannulation?
Settings: Hospital

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrous oxide + EMLA	EMLA	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/25 (100%)	21/21 (0%)	RR 1.19 (0.99 to 1.43)	0 more per 1,000	VERY LOW	

[1] Randomisation and allocation concealment not well explained. Blinding not possible.
[2] Small study with no power calculations.

COMBINATION COMPARISONS

Table 57: Nitrous oxide + IV midazolam vs. medical air + IV midazolam; Averley 2004[20]

Author(s): Averley 2004[20]
Question: 40% Nitrous oxide plus intravenous midazolam vs. medical air for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV midazolam & 40% Nitrous oxide	medical air + IV midazolam	Relative (95% CI)	Absolute		
Completion of procedure: nitrous oxide vs. medical air												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204/256 (79.7%)	94/176 (53.4%)	RR 1.49 (1.28 to 1.74)	261 more per 1,000	MODERATE	
Pain by VAS score: nitrous oxide vs. medical air (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	204	94	-	MD 0 (-0.28 to 0.28)	MODERATE	
Recovery time: nitrous oxide vs. medical air (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204	94	-	MD -0.8 (-2.03 to 0.43)	MODERATE	
Anxiety: nitrous oxide vs. medical air (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204	94	-	MD 0 (-0.32 to 0.32)	MODERATE	

[1] Greater than 20% did not complete intervention; greater in 1 group and this group of the study was discontinued

Table 58: Nitrous oxide + IV midazolam vs. nitrous oxide + IV midazolam + sevoflurane and; Averley 2004[20]

Author(s): Averley 2004[20]
Question; 40% nitrous oxide plus intravenous midazolam vs. 0.3% sevoflurane and 40% nitrous oxide for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV midazolam & 40% nitrous oxide	0.3% sevoflurane and IV midazolam & 40% nitrous oxide	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204/256 (79.7%)	249/267 (93.3%)	RR 0.85 (0.8 to 0.92)	139 fewer per 1,000	MODERATE	
Pain: VAS scale (range of scores: -; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204	249	-	MD 0 (-0.24 to 0.24)	MODERATE	
Recovery time (range of scores: -; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204	249	-	MD -0.5 (-1.21 to 0.21)	MODERATE	
Anxiety (range of scores: -; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	204	249	-	MD 0 (-0.24 to 0.24)	MODERATE	

[1] 20% of nitrous oxide group failed to complete procedure and are not included in further analysis.

Table 59: Nitrous oxide + midazolam + sevoflurane vs. medical air + midazolam; Averley 2004[20]

Author(s): Averley 2004[20]
Question 40% nitrous oxide and 0.3% sevoflurane & plus intravenous midazolam vs. medical air for sedation in children
Settings: Dental

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV midazolam & 3%sevoflurane and 40% nitrous oxide	medical air	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	249/267 (93.3%)	94/174 (54%)	RR 1.73 (1.5 to 1.99)	394 more per 1,000	MODERATE	
Pain: VAS scale (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	249	94	-	MD 0.4 (-0.31 to 0.31)	MODERATE	
Recovery time (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	249	94	-	MD -0.3 (-1.82 to 1.22)	MODERATE	
Anxiety (range of scores: Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	249	94	-	MD 0.8 (-0.31 to 0.31)	MODERATE	

[1] Greater than 20% of children did not complete procedure and group 1 (medical air) was terminated. Secondary analyses done only for those completing procedure.

6.7.2.2Non RCT safety (adverse events) for nitrous oxide

Three non RCT observational studies assessed the safety of nitrous oxide in a total of 8,220 patients. Two prospective cohort studies with greater than 100 subjects specifically assessed the safety of nitrous oxide[21,73]. One systematic review which contained information from two relevant paediatric RCTs was also included[61].

The non RCT study characteristics for nitrous oxide are presented in Table 60.

The non RCT adverse event table for nitrous oxide are presented in Table 61.

1 **Table 60: Nitrous oxide Non RCT study characteristics. Safety review**

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Prospective Cohort						
Babl et al, 2008[22] Australia	Tertiary children's hospital emergency department		Procedural sedation	60%	70% nitrous oxide – 72% patients 50% nitrous oxide – 28%	2 hours
Gall et al, 2001[73] France	French hospitals; records of paediatric procedures		Procedural sedation with 50% nitrous oxide		50% nitrous oxide	
Retrospective Systematic Review- 12 RCTs (2 paediatric studies with outcomes of interest)						
Faddy & Garlick, 2005[61] Australia	Paediatric Emergency Department Laceration repair; fracture reduction		Procedural sedation		50% nitrous oxide	

Table 61: Nitrous oxide safety: Non RCT

Study type, reference, country	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)								GRADE PROFILE
					Aspiration	Respiratory intervention			Cardiac arrest requiring either/or		vomiting	oxygen saturation <90%	EVIDENCE QUALITY
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
Prospective Cohort studies													
Babel et al, 2008[21] Australia	70% nitrous oxide	Emergency procedures	0-18 years	72% (548)							4.7% (26/548)	0.18% (1/548)	VERY LOW
	50% nitrous oxide			13% (101)							3.9% (4/101)	0	VERY LOW
Gall et al, 2001[73] France	50% nitrous oxide	Emergency procedures including laceration repair, fracture reduction, cast remodelling, abscess drainage, lumbar puncture, dressing changes, bone-marrow aspiration, flexible bronchoscopy, gastroscopy, venous puncture and	<19 years	7511* Adverse events reported as 'major' or 'minor' (terms not defined). 375 minor events (5%) and 25 major events (0.3%) All major events resolved within minutes after discontinuation of nitrous oxide. No patient needed		0	0	0					VERY LOW

		other miscellaneous procedures		intervention to maintain their airway.									
Retrospective Systematic Review- 12 RCTs (2 paediatric studies with outcomes of interest)													
Faddy & Garlick, 2005[61] Australia	50% nitrous oxide	Laceration repair; fracture reduction;	Mean age Study 1 (Burton et al, 1998): 3.7 (SD 1.6) years. Study 2 (Evans et al 1995) 10 (4-15) years	60							0	0	VERY LOW

6.7.3 Evidence statements for nitrous oxide

6.7.3.1 RCT efficacy and safety for nitrous oxide

PLACEBO COMPARISONS

Nitrous oxide vs. oxygen

McCann 1996[161]

There was no significant difference in:

- Quiet behaviours [low quality evidence]

Nitrous oxide vs. oxygen

Primosch 1999[187]

Compared to 100% oxygen, the nitrous oxide group had significantly:

- More quiet behaviours [low quality evidence]

There was no significant difference between nitrous oxide/oxygen vs. 100% oxygen groups for the following variable:

- Oxygen saturation [low quality evidence]

Nitrous oxide vs. nitrogen and oxygen

Fauroux 2004[64]

Compared to 50% nitrogen and oxygen, the nitrous oxide group had significantly:

- Fewer procedure failures [low quality evidence]
- Less pain immediately after the procedure as measured on the CHEOPS scale [low quality evidence]
- Less pain (children >6 years old) immediately after the procedure as measured on a VAS scale [low quality evidence]

HEAD TO HEAD COMPARISONS

Nitrous oxide vs. behavioural management

Veerkamp 1993[224]*; Veerkamp 1995*[222]

Two studies by the same authors with similar research methods and outcomes were meta-analysed. Anxiety was the only outcome of interest measured in this study. Behavioural observations were made using the Venham clinical rating scale.

Compared with behavioural management, the nitrous oxide group had significantly

- Less anxiety than the behavioural management group [very low quality evidence]

Nitrous oxide vs. transmucosal midazolam

Wilson 2007[235]

Compared to transmucosal midazolam, the nitrous oxide group had significantly:

- Less induction time [low quality evidence]
- Less procedure time [low quality evidence]
- Less total time [low quality evidence]
- More patients preferred nitrous oxide sedation [low quality evidence]

Nitrous oxide vs. IV midazolam

Wilson 2003[231]

Compared to IV midazolam, the nitrous oxide group had significantly:

- Shorter induction time [low quality evidence]
- Shorter procedure time [low quality evidence]
- Shorter total time [low quality evidence]
- Shorter recovery time [low quality evidence]

There was no significant difference in:

- Patient preference [low quality evidence]

Nitrous oxide vs. oral midazolam

Wilson 2006; Wilson 2002; Wilson 2002[232-234]

Compared to oral midazolam, the nitrous oxide group had significantly:

- Shorter induction time [moderate quality evidence]
- Shorter procedure time in one study [moderate quality evidence]
- Shorter recovery time [moderate quality evidence]
- Shorter total time [moderate quality evidence]

There was no significant difference in:

- Procedure time in two studies [moderate quality evidence][233,234]
- Patient preferences [moderate quality evidence] when the results of two studies were meta analysed[233,234]. The results of Wilson 2006[232] were non significant but data was not available for meta-analysis.

Nitrous oxide + EMLA vs. EMLA

Ekbom 2005[58]

Compared to conventional treatment for intravenous cannulation with EMLA anaesthetic cream, children who received nitrous oxide + EMLA were reported by the authors to have a statistically significant difference in the following parameter:

- Pain as assessed by VAS [Very low quality].

There was no significant difference in:

- Completion of procedure [Very low quality].

COMBINATION COMPARISONS

Averley 2004[20]

Nitrous oxide + IV midazolam vs. medical air + IV midazolam;

Nitrous oxide + IV midazolam vs. sevoflurane and nitrous oxide + IV midazolam

Nitrous oxide + IV midazolam and sevoflurane vs. medical air + IV midazolam

a) 40% nitrous oxide + IV midazolam vs. medical air + IV midazolam

Compared to the medical air group, the nitrous oxide group had significantly:

- More completed procedures [moderate quality evidence]

There were no significant differences in:

- Recovery time [moderate quality evidence]
- Pain by VAS score [moderate quality evidence]
- Anxiety by VAS score [moderate quality evidence]

b) 40% nitrous oxide + IV Midazolam vs. 0.3% sevoflurane and 40% nitrous oxide + IV midazolam

Compared to the sevoflurane group, the nitrous oxide group had significantly:

- Fewer completed procedures [moderate quality evidence]

There were no significant differences in:

- Recovery time [moderate quality evidence]
- Pain by VAS score [moderate quality evidence]
- Anxiety by VAS score [moderate quality evidence]

c) 0.0.3% sevoflurane and 40% nitrous oxide + IV Midazolam vs. medical air + IV midazolam

Compared to the medical air group, the sevoflurane + nitrous oxide group had significantly:

- More completed procedures [moderate quality evidence]

There were no significant differences in:

- Recovery time [moderate quality evidence]
- Pain by VAS score [moderate quality evidence]
- Anxiety by VAS score [moderate quality evidence]

Adverse events were reported for all three arms of this study as follows:

- Six children in the sevoflurane group vomited clear fluids after treatment [moderate quality evidence]
- 98% of all children had an oxygen saturation of 98% or above. The lowest saturation of 94% was recorded in one child in the medical air group [moderate quality evidence]

6.7.3.2NON-RCT safety (adverse events)

- There were no reported incidents requiring respiratory intervention including an oral pharyngeal airway, endotracheal intubation or assisted ventilation[21,61,73].

- There were no reported incidents of cardiac arrest requiring either/or external cardiac massage or defibrillation[21,61,73].
- One study reported a 4.7% rate of vomiting with 70% nitrous oxide and a 3.9% rate of vomiting with 50% nitrous oxide[22]
- One study reported oxygen saturation <90% in0.18% of patients using 70% nitrous oxide[22]. Two studies using 50% nitrous oxide reported that there were no patients with oxygen saturation <90%[21,61].

6.7.4 GDG discussion of the evidence for nitrous oxide

The GDG noted that most of the evidence for nitrous oxide came from studies of painful procedures in the Emergency Department or the Dental clinic settings. The evidence level was low except in one RCT where the level was moderate.

The GDG agreed that both the efficacy and safety may be dependent on the concentration of nitrous oxide used. In almost all studies the dose was 50% or less in oxygen. Seventy percent oxygen was reported in a non-RCT in the ED setting.

The GDG noted that the evidence of efficacy in the RCTs was limited to the successful outcome of the procedure and that there were no data to allow the quality of the sedation to be assessed.

The GDG recognised that nitrous oxide is very widely used in UK dental clinics and it was appreciated that the success of administration of nitrous oxide relies on ability of the patient to breathe the gas continuously via a mask placed over the mouth and nose, or over the nose for dental procedures. Gaining and maintaining cooperation of a patient also relies on the skill of the healthcare practitioners.

In small uncooperative children nitrous oxide was not found to be any more effective than oxygen alone[161] but in cooperative children nitrous oxide could be used for a wide range of painful procedures provided the analgesia of the nitrous oxide was sufficient. In the dental setting the injection of local anaesthesia can be uncomfortable and the analgesia from nitrous oxide is effective for the local anaesthesia; thereafter, the value of nitrous oxide may relate to its euphoric and anxiolytic effect. The success rate of nitrous oxide in the dental setting was reported as approximately 50% and it was appreciated that this success rate was poor. Nevertheless it was argued by the dentists on the GDG that these studies were in children who had been referred to a dental clinic that specialised in the management of anxious children. In other dental clinics, where children may be less anxious, the success rate was considered to be much higher although no direct evidence was available to support this. Moreover the GDG dentists confirmed that children could be selected into those in whom nitrous oxide would and would not be sufficient for dental treatment; in their experience the success rate of nitrous oxide in selected children was at least 90%.

The advantages of nitrous oxide were considered to be that it was well tolerated and short acting and highly effective in selected patient groups and settings. Occasionally it causes dysphoria and vomiting but this may be related to higher concentrations of nitrous oxide. The GDG appreciated the potential economic advantages of nitrous oxide successfully delivered in the dental clinic setting rather than anaesthesia in the dental hospital setting.

The GDG considered the safety of nitrous oxide. It was agreed that it was extremely unlikely that nitrous oxide concentration of 50% or less would cause unconsciousness provided the patient was fully conscious beforehand and that no other sedation drugs were used. Equipment failure and medical contraindications to the use of nitrous oxide are rare but the GDG agreed that patients must be assessed and that practitioners must be trained to use nitrous oxide safely. The GDG agreed that nitrous oxide (used alone) had a good tolerability record and that fasting was not required (although nitrous oxide may induce vomiting if the stomach was full) and that it could be safely administered by the dentist who was treating the patient.

The GDG debated the merits of combining nitrous oxide with other drugs to increase its efficacy. One RCT[20] showed 80% of anxious children undergoing dental procedures were treated successfully by a combination of nitrous oxide with midazolam compared with only 54% of children with midazolam alone. In that study the combination of drugs did not cause unconsciousness but the GDG discussed the risk of unconsciousness caused by combining drugs. It was appreciated that intravenous and inhalational drugs could be titrated to achieve conscious sedation and that unconsciousness was extremely unlikely provided the dental sedation team were skilled. Nevertheless it was agreed that there was a risk of unintended unconsciousness and that only specially trained dental sedation teams should use combinations of sedation drugs to achieve sedation. The GDG agreed that airway management skills and equipment are essential for combining nitrous oxide with other sedation drugs.

The general principle agreed by the GDG is that only sedation techniques commonly available in the NHS should be included in the economic analysis. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). The GDG agreed that nitrous oxide alone, and nitrous oxide combined with other drugs (nitrous oxide plus sevoflurane, nitrous oxide plus sevoflurane plus midazolam, and nitrous oxide plus midazolam) are commonly used in dental procedures in children, and that there is some evidence that they are effective and well tolerated. It was therefore agreed that these strategies should be included in the economic analysis. Details of the considerations of cost-effectiveness with respect to using these strategies in dental procedure in children are given in section 6.12.4.2.

6.8 Sevoflurane and isoflurane

Matrix of sevoflurane / isoflurane comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Isoflurane = I
Ketamine=K
Midazolam = M
Propofol= P
Nitrous oxide = $N_2$0
Nitrous oxide and oxygen = $N_2$0+02
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Sevoflurane / isoflurane vs

	Reference	Tables and page	Evidence statements page
Placebo			
Nil			
Head to head			
Nil			
Combinations			
S + NO + M vs. air + M	Averley 2004[20]	Table 62	273
S + NO + M vs. NO + M	Averley 2004[20]	Table 63	273
S + NO + vs. NO	Lahoud 2002[134]	Table 64	273
Safety			
RCTs			
Desaturation	Lahoud 2002[134]	Table 65 Table 66	274
Vomiting	Averley 2004[20]	Table 65 Table 66	274
Observational studies	De Sanctis Briggs 2005[51]	Table 65 Table 66	274

Route of administration			
Nil			
Dose			
Nil			

6.8.1 Clinical methodological introduction for sevoflurane or isoflurane

CLINICAL QUESTIONS

For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is sevoflurane or isoflurane (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?

- Safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy of sevoflurane or isoflurane. The search was expanded to include non RCT observational studies for the safety of sevoflurane or isoflurane.

There were no systematic reviews identified for the use of sevoflurane or isoflurane in paediatric sedation.

Two RCTs comparing sevoflurane in any route with other sedative drugs were assessed for efficacy and safety.

One non RCT observational study in 640 patients assessed the safety of sevoflurane.

There were no relevant studies conducted in children that assessed the safety and efficacy of sedation with isoflurane.

Meta-analyses for RCTs were performed where drug interventions and comparisons and outcomes were sufficiently homogenous and studies were combined regardless of dose, duration of intervention, procedure (within painful and non-painful groups), setting (e.g. dentistry, accidents and emergencies) and age.

6.8.2 Evidence profiles for sevoflurane or isoflurane

6.8.2.1 RCT evidence profiles for efficacy and safety for sevoflurane or isoflurane

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

COMBINATION COMPARISONS

Table 62: Sevoflurane + nitrous oxide + intravenous midazolam vs. medical air + intravenous midazolam; Averley 2004[20]

Question: Should sevoflurane + nitrous oxide + iv midazolam titrated vs. medical air + iv midazolam titrated be used for sedation in children?
Settings: dental hospital

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	sevoflurane + nitrous oxide + iv midazolam titrated	medical air + iv midazolam titrated	Relative (95% CI)	Absolute		
number of people who complete procedure												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249/267 (93.3%)	94/174 (54%)	RR 1.73 (1.5 to 1.99)	394 more per 1000 (from 270 more to 535 more)	HIGH	
Recovery time (Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	94	-	MD -0.3 (-1.55 to 0.95)	MODERATE	
child's perception of pain (VAS score) (measured with: VAS; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	94	-	MD 0 (-0.28 to 0.28)	MODERATE	
Anxiety reported by child (VAS score) (measured with: VAS; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	94	-	MD 0 (-0.31 to 0.31)	MODERATE	
Parent's satisfaction score (range of scores: 1-5; Better indicated by more)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	94	-	MD 0.1 (-0.05 to 0.25)	MODERATE	
vomiting												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/249 (2.4%)	0/94 (0%)	RR 4.94 (0.28 to 86.84)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	

[1] double blind with adequate allocation concealment and randomisation; ITT was performed for this outcome.
[2] double blind with adequate allocation concealment and randomisation; ITT was not performed for this outcome.
[3] very wide 95% CI

Table 63: Sevoflurane + nitrous oxide + intravenous midazolam vs. nitrous oxide + intravenous midazolam; Averley 2004[20]

Question: Should sevoflurane + nitrous oxide + iv midazolam titrated vs. nitrous oxide + iv midazolam titrated be used for sedation in children?
Settings: dental hospital

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	sevoflurane + nitrous oxide + iv midazolam titrated	nitrous oxide + iv midazolam titrated	Relative (95% CI)	Absolute		
number of people who complete procedure												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249/267 (93.3%)	204/256 (79.7%)	RR 1.17 (1.09 to 1.25)	135 more per 1000 (from 72 more to 199 more)	HIGH	
Recovery time (Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	204	-	MD 0.5 (-0.21 to 1.21)	MODERATE	
child's perception of pain (VAS score) (measured with: VAS; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	204	-	MD 0 (-0.24 to 0.24)	MODERATE	
Anxiety reported by child (VAS score) (measured with: VAS; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	204	-	MD 0 (-0.24 to 0.24)	MODERATE	
Parent's satisfaction score (range of scores: 1-5; Better indicated by more)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	204	-	MD 0 (-0.1 to 0.1)	MODERATE	
vomiting												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/249 (2.4%)	0/204 (0%)	RR 10.66 (0.6 to 188.11)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	

[1] double blind with adequate allocation concealment and randomisation; ITT for this outcome
[2] double blind with adequate allocation concealment and randomisation; ITT was not performed for this outcome.
[3] very wide 95% CI

Table 64: Sevoflurane + nitrous oxide vs. nitrous oxide; Lahoud 2002[134]

Question: Should sevoflurane + nitrous oxide vs. nitrous oxide be used for sedation in children?
Settings: dental hospital

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	sevoflurane + nitrous oxide	nitrous oxide	Relative (95% CI)	Absolute		
number of children who complete procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/241 (89.2%)	89/170 (52.4%)	RR 1.7 (1.47 to 1.98)	367 more per 1000 (from 246 more to 514 more)	MODERATE	
number of children who had a score of anxiety (Venham score = 5) (Venham score)												
1	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/215 (0%)	2/89 (2.2%)	RR 0.08 (0 to 1.72)	20 fewer per 1000 (from 22 fewer to 16 more)	VERY LOW	
Number of children who were satisfied with the treatment (rated treatment as excellent)												
1	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	188/215 (87.4%)	74/89 (83.1%)	RR 1.05 (0.95 to 1.17)	42 more per 1000 (from 42 fewer to 141 more)	LOW	
Adverse events: Oxygen desaturation <90%												
1	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/215 (100%)	0/89 (100%)	not pooled	-	LOW	

[1] unclear if assessor was blind and no detail on randomisation generation; adequate allocation concealment; ITT analysis performed for this outcome
[2] unclear if assessor was blind and no detail on randomisation generation; adequate allocation concealment; ITT analysis was not performed for this outcome
[3] very wide 95% CI

6.8.2.2Non RCT evidence profiles for safety for sevoflurane or isoflurane

One non-RCT observational study (n=640) assessed the safety of sevoflurane[51].

The non RCT study characteristics for midazolam are presented in Table 65.

The non RCT adverse event table for midazolam is presented in Table 66.

Table 65: Sevoflurane Non RCT Study Characteristics Safety Review

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
De Sanctis Briggs 2005[51], Spain	Centre for MRI	Not stated	Deep Sedation for MRI examinations N= 640 infants age 1 day – 12 months	46.5%	Inhaled sevoflurane 7% in 50% nitrous oxide for induction; followed by sevoflurane 1.8-2% in 50% nitrous oxide for maintenance	Sedation fasting protocol

Table 66: Sevoflurane Safety: Non RCTs

Study type, reference, country	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)								GRADE PROFILE
					Aspiration				Cardiac arrest requiring either/or		vomiting	oxygen desaturation <90%	EVIDENCE QUALITY
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
De Sanctis Briggs 2005[51], Spain	sevoflurane 1.8-2% in 50% nitrous oxide	MRI	1 day – 12 months old 15% < 1 month old 39% 1-6 months old 45% 7-12 months old	640 They state that 627/640 (97.9%) of patients experienced no complications (defined as vomiting, mild or severe hypoxia, prolonged sedation, or agitation							1/640 = 0.16%	0/640 = 0%	VERY LOW

6.8.3 Evidence statements for sevoflurane or isoflurane

6.8.3.1 RCT efficacy and safety for sevoflurane or isoflurane

COMBINATION COMPARISONS

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

Averley, 2004[20]

Compared with medical air and intravenous midazolam group, the sevoflurane + nitrous oxide + intravenous midazolam group had significantly:

- More completed procedures [high quality evidence]

There was no significant difference in:

- Recovery time [moderate quality evidence]
- Child's perception of pain score (VAS) [moderate quality evidence]
- Anxiety reported by child (VAS) [moderate quality evidence]
- Vomiting [very low quality evidence]

Sevoflurane + nitrous oxide + IV midazolam vs. nitrous oxide + IV midazolam

Averley, 2004[20]

Compared with nitrous oxide + intravenous midazolam group, the sevoflurane + nitrous oxide + intravenous midazolam group had significantly:

- More completed procedures [high quality evidence]

There was no significant difference in:

- Recovery time [moderate quality evidence]
- Child's perception of pain (VAS) [moderate quality evidence]
- Anxiety reported by child (VAS) [moderate quality evidence]
- Parent's satisfaction score (scale 1-5) [moderate quality evidence]
- Vomiting [very low quality evidence]

Sevoflurane + nitrous oxide vs. nitrous oxide

Lahoud 2002[134]

Compared with the nitrous oxide group, the sevoflurane + nitrous oxide group had significantly:

- More completed procedures [moderate quality evidence]

There was no significant difference in:

- Anxiety (proportion of patients) (Venham score = 5) [very low quality evidence]

There were no events of:

- Oxygen saturation < 90% [low quality evidence]

6.8.3.2Non RCT safety (adverse events) for sevoflurane or isoflurane

For the characteristics of studies and outcome data refer to Table 65 and Table 66.

One study[51] reported rates of:

- Vomiting: 0.16%
- Oxygen desaturation <90%: 0%

6.8.4 GDG discussion of the evidence for sevoflurane and isoflurane

Three studies[20,51,134] informed the GDG discussion on sevoflurane. Sevoflurane is an anaesthetic agent and the GDG discussed whether there was an appreciable risk of accidental anaesthesia. Two[20,134] of the three studies were RCTs in which sevoflurane had been used to sedate anxious children for dental procedures in a specialist dental clinic. The GDG appreciated that sevoflurane was being used in a similar fashion to nitrous oxide in that it required the patient to tolerate breathing the vapour via a nasal mask. In low doses sevoflurane was reported to not cause anaesthesia and its success therefore relied on a degree of cooperation of the patient. The dental studies were in anxious children up to the age of 14. Concentrations of up to 0.3% were used with (or without) 40% nitrous oxide and also with intravenous midazolam titrated to achieve satisfactory compliance for the dental procedure. The addition of sevoflurane was found to increase the completion rate of dental treatment.

The GDG agreed that this is a successful technique but that it required special expertise of a trained sedation team, and that airway management skills and equipment are essential for this drug in this setting.

The other study[51] considered was a descriptive account of 640 infants who were sedated by a combination of sevoflurane and nitrous oxide for painless imaging. The dose of sevoflurane used was 1.8-2% and even though the GDG understood that the conscious level had not been tested, the GDG decided that it was very likely that the infants had been anaesthetised by this dose.

The GDG discussed the advantages of sevoflurane sedation over sevoflurane anaesthesia. In certain settings, in which the patient needs to cooperate with a procedure, such as a dental procedure, sedation may be appropriate. In other situations, such as painless imaging where an uncooperative child needs to be immobile and asleep, the dose of sevoflurane required to cause sleep is likely to cause anaesthesia. The GDG agreed that it was safer to assume that that patients were anaesthetised in this setting and that they would therefore need to managed as though they had a short acting anaesthetic rather than sedation. Overall the GDG agreed that sevoflurane should only be used by specially trained sedation teams.

The GDG agreed that only sedation techniques commonly available in the NHS should be included in the economic analysis. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). Sevoflurane combined with other drugs (sevoflurane plus nitrous oxide, sevoflurane plus nitrous oxide plus midazolam) were felt to be strategies commonly used in dental procedures in children. There is evidence that these drug combinations are effective and well tolerated. The GDG therefore agreed that they should be included in the economic analysis. Details of the considerations of cost-effectiveness with respect to using these combination strategies in dental procedures in children are given in section 6.12.4.2.

6.9 Propofol

Matrix of propofol comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Isoflurane = I
Ketamine=K
Local anaesthesia = LA
Midazolam = M
Nitrous oxide = N_20
Nitrous oxide and oxygen = N_20+0_2
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Propofol vs

	Reference	Tables	Evidence statements page
Placebo			
Nil			
Head to head			
Nil			
Combinations			
P vs. M + K + F	Vardi 2002[221]	Table 61	290
Safety			
RCTs			
Assisted ventilation	Vardi 2002[221]	Table 68 Table 69	290
ET intubation	Vardi 2002[221]	Table 68 Table 69	290
Observational studies	Melamed 1976[167] Bassett 2003[26] Barbi 2006[25] Vespasiano 2007[226] Larsen 2009[135] Cravero 2009[46] Barbi 2003[24]	Table 68 Table 69	290

Route of administration			
Nil			
Dose			
Nil			

6.9.1 Clinical methodological introduction for propofol

CLINICAL QUESTIONS:

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?

- Safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy of propofol. The search was expanded to include non-RCT observational studies for the safety of propofol.

There were no systematic reviews identified for the use of propofol in paediatric sedation.

One RCT comparing intravenous propofol with other sedative drug was assessed for efficacy and safety.

Seven non-RCTs observational studies in 64,115 patients assessed the safety of intravenous propofol.

Meta-analyses were not performed as there was only one RCT.

6.9.2 Evidence profiles for propofol

6.9.2.1 RCT evidence profiles for efficacy and safety for propofol

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

COMBINATION COMPARISONS

Table 67: Intravenous propofol + propofol maintenance + local anaesthesia vs. intravenous midazolam + intravenous ketamine + intravenous fentanyl ; Vardi 2002[221]

Question: Should intravenous propofol plus propofol maintenance plus local anaesthesia vs. intravenous midazolam plus intravenous ketamine plus intravenous fentanyl be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: paediatric critical care unit (convenient facility for procedures)
Bibliography: Vardi 2002[221] (mixed procedures: Intraarticular steroid injection, bronchoscopy, bone marrow aspiration/biopsy, transesophageal echocardiography, PEG/Gastroscopy, Other: central line placement, intrathechal injections, removal of tunnelled central venous catheter, wound care, and chest tube placement)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous propofol plus propofol maintenance plus local anaesthesia	intravenous midazolam plus intravenous ketamine plus intravenous fentanyl	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/58 (100%)	47/47 (100%)	not estimable	-	LOW	
1	randomised trial											
Duration of procedure (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	47	-	MD -2 (-9.28 to 5.28)[3]	LOW	
Recovery time: from administration of last sedation dose to when patients opened their eyes or gave appropriate response (Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	47	-	MD -27 (-35.22 to -18.78)[4]	LOW	
Satisfaction at induction period assessed by four observers (paediatric nurse, resident physician, paediatric intensivist delivering sedation, physician performing procedure) using a validated scale (measured with: Ramsay scale (maximum score = 6) at induction period; range of scores: 1-6; Better indicated by more)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	58	47	-	MD 0.26 (-0.08 to 0.59)[6] MD 0.26 (-0.08 to 0.59)	VERY LOW	
Satisfaction at sedation period assessed by four observers (paediatric nurse, resident physician, paediatric intensivist delivering sedation, physician performing procedure) using a validated scale (measured with: Ramsay scale (maximum score = 6) at procedure period; range of scores: 1-6; Better indicated by more)												

1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	58	47	-	MD 0.25 (0.03 to 0.47)[7]	VERY LOW	
Adverse events: Assisted ventilation: bag/mask												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	10/58 (17.2%)	3/47 (6.4%)	RR 2.70 (0.79 to 9.26)[9]	109 more per 1000 (from 13 fewer to 529 more) 0 more per 1,000	VERY LOW	
Adverse events: Endotracheal intubation												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/58 (0%)	1/47 (2.1%)	RR 0.27 (0.01 to 6.51)[10]	15 fewer per 1000 (from 21 fewer to 116 more) 0 fewer per 1,000	VERY LOW	

[1] Vardi 2002[221]: concealment and ITT not stated and blinding of patients and assessors not stated or unclear; small study
[3] Vardi 2002[221]: p=0.59
[4] Vardi 2002[221]: p<0.00001
[5] Vardi 2002[221]: imprecise
[6] Vardi 2002[221]: p=0.13
[7] Vardi 2002[221]: p=0.03
[8] Vardi 2002[221]: imprecise and too wide confidence intervals; small study
[9] Vardi 2002[221]: p=0.11
[10] Vardi 2002[221]: p=0.42

6.9.2.2 Non RCT evidence profiles for safety for propofol

Seven non RCT observational studies (n=64,115) assessed the safety of propofol[24-26,46,135,168,226] There were six prospective studies, and one retrospective study conducted for the following procedures: imaging procedures (2), accidents and emergencies procedures (1) as well for GI and oncology procedures (2) and inpatients and outpatients (2).

The non RCT study characteristics for midazolam are presented in Table 68.

The non RCT adverse event table for midazolam is presented in Table 69.

1 **Table 68: Propofol Non RCT Study Characteristics Safety Review**

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Merola 1995[168], USA	Imaging (MRI and CT suites) (99% ambulatory)	I-II Other ASA I-II: 99.34% (452/455) Other: 0.66% (3/455)	Not stated	Not stated	PRO or CH: PRO: • 2 mg/kg bolus after iv access + dilute PRO by gravity titrated infusion at a rate of 80-140 mcg/kg/min • Children ≥1 y.o. generally received PRO unless they had poor venous access or unless there was a strong parental preference for not inserting an i.v. catheter CH: • Children <1 y.o. generally received CH 75 mg/kg to a maximum of 2g due to difficulty in establishing i.v. access • Younger children were often swaddled and provided with a pacifier • Parents accompanied the children Concurrent: • All patients received O2 at 2 L/min by nasal cannule during procedures (scans)	Not stated
Barbi 2003[24], Italy	Paediatric sedation unit (admitted to paediatric gastroenterology and oncology wards)	I-II	Deep (91% (963/1059) of children experienced transient general anaesthesia at any	50% (411/827)	LA/TA/Atropine/PRO/GlucoSol LA: Lidocaine/prilocaine: • 1 to 10 mg Lido/PRO for 1st syringe in children without a central line TA: EMLA cream	Clear fluids not allowed for 3 hrs, infant formula and nonhuman milk for 6 hours and solids for 8 hours

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
			time during the procedure)		Atropine: 0.01 mg/kg as premedication PRO: • 2mg/kg in children ≤8 y.o. • 1 to 2 mg/kg in >8 y.o. • repeated dose 0.5-1 mg/kg or continuous 6-9 mg/kg per hour for long procedures GlucoSol: continuous infusion maintenance Concurrent: O2 administered after the 2nd year of study at 6L/min by mask close to face to anticipate hypoxemia; O2 was administered during procedure from beginning of study for children undergoing painful procedures mostly those with cancer	
Bassett 2003[26], USA	Emergency department	I-II ASA I: 96% (379/393 procedures) ASA II: 4% (14/393 procedures)	Procedural sedation	67% (263/392)	PRO/Opioid analgesics: PRO: • IV initial dose of 1mg/kg (max 40 mg); • IV supplemental doses of 0.5 mg/kg (max 20 mg) at discretion of physician • Bolus over 1 to 2 min, 20 secs between each dose; titrated to tolerance of noxious stimuli without patient complaint Morphine: • 0.1 mg/kg (max 5 mg) for	Minimum of 3 hrs for solids and liquids

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
					significant pain on presentation to emergency department Fentanyl: • 1 to 2 mcg/kg (max 50 mcg) for children who had not received narcotics or were still with significant pain Concurrent: supplemental O2 at 10 L/min with a bag-valve mask to face before initiation and during procedure; not used for assistance with respirations unless requested by physician and suction available at bedside	
Barbi 2006[25], Italy	Department of gastroenterology (Endoscopic room)	I-II	Procedural sedation	47% (337/716)	TA/Atropine/IV PRO/LA/GlucoSol or Ringer'sSol TA: EMLA cream Atropine: 0.010-0.015 mg/kg PRO infusion: • in children up to 8 y.o.:2mg/kg • in children >8 y.o.:1-2 mg/kg • repeated dose 0.5-1 mg/kg or continuous 6-9 mg/kg per hour for long procedures LA: lidocaine 1 mg for every 10 mg of PRO for the first syringe in all children GlucoSol: continuous infusion maintenance (for age and weight) for children >5 y.o. Concurrent:	Clear fluids not allowed for 3 hrs, infant formula and nonhuman milk for 6 hrs and solids for 8 hrs

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
					O2 administered after the 2nd year of study at 6L/min by mask close to face to anticipate hypoxemia; O2 was administered during procedure from beginning of study for children undergoing painful procedures mostly those with cancer	
Vespasiano 2007[226], USA	MRI 42.8% (3126/7304), radiology 22.5% (1643/7304), short stay unit 26.2% (1914/7304), special diagnostics unit 4.3% (314/7304), PICU 2% (146/7304), Other 2.2% (161/7304)	ASA I-II: 99.7% (7285/7304) ASA > II: 2.5% (18/7304) ASA unassigned: 0.014% (1/7304)	Deep	Not stated	PRO/PRO maintenance/LA PRO: • rarely <2 mg/kg • intermittent bolus doses for shorter interventions and continuous infusion after initial bolus for longer interventions • continuous infusion initiated at 150 mcg/kg/min titrated as required PRO maintenance: • supplemental boluses 1-2 mg/kg LA: • lidocaine doses at discretion of intensivist Concurrent: • O2 supplementation is administered to all patients who receive propofol	Not stated

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Larsen 2009[135], USA	Database established by paediatric intensive care to track outpatients requiring propofol sedation for diagnostic therapeutic procedures Retrospective analysis of database to track each outpatient paediatric procedure requiring propofol	Not stated	Not stated	52% (2463/4716)	• Intravenous propofol sedation sufficient to reach a level of sedation not requiring endotracheal intubation	Not stated
Cravero 2009[46], USA	Outside the operating room Collaborative database of adverse events from 37 locations with data on paediatric sedation/anaesthesia. Prospectively enrolled consecutive patients receiving sedation or sedation/anaesthesia for procedures. Primary inclusion was the need for some form of sedation/anaesthesia to perform a diagnostic or therapeutic procedure outside the operating room.	ASA ≤ II (41191/49836) ASA > II 18% (8915/49836)	Not clear whether propofol was used for sedation or anaesthesia	55% (27420/48836)	Not clear	Not stated

Table 69: Propofol Safety: Non RCTs

Study type, reference, country	**Drug / Comparison**	**Procedure**	**Age**	**Total N**	**ADVERSE EVENTS, rate: % (n)**								**GRADE PROFILE**
					Aspiration				Cardiac arrest requiring either/or		vomiting	oxygen desaturation <90%	EVIDENCE QUALITY
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
Merola 1995[168], USA	Propofol/O2 and Chloral Hydrate/O2	Scans of the head, thorax, abdomen, pelvis and spine	Overall age range: <1 mo to 17y PRO range: <1 mo- to 17y ≥1 y: 98% (318/324) <15y: 4% (13/324) CH range: <1 mo to 7 y <1 y: 51% (57/131)	Total: 455 324 PRO 131 CH		0% (airway compro-mise)	0%	0% (controlled ventilation)			0%		VERY LOW
Bassett 2003[26], USA	Propofol/Mo or Fentanyl (analgesics)	Fractures (96%: 378/393 procedures) Dislocations (3.6%: 14/393 procedures) Examination of ocular burn (0.25%: 1/393 procedures)	Overall age range: 1 to 18y Median age: 8 y	393 procedures in 392 children (1 child sedated twice)	0%	3% (11/392) (partial airway obstruct-tion)	0%	0.8% (3/392) (bag-valve-mask)	0% (cardiopulmonary arrest)			5% (20/392)	VERY LOW
Barbi 2003[24], Italy	LA/ TA/Atropine/ Propofol	Upper endoscopies, colonoscopies, painful procedures	<1y to <10y: 61% (503/827) 10y to <21y:	Total: 1059 procedures in 827 children				Total: 0.5% (5/1059 procedures)			1.05% (3/827) (repeated vomiting	6.04% (64/1059 procedures)	VERY LOW

			39% (324/827)	upper endoscopy: 483 procedures in 405 children colonoscopy: 289 procedures in 249 children painful: 287 procedures in 173 children				endoscopies 0.83% (4/483 procedures) colonoscopies 0% (0/289 procedures) painful 0.35% (1/287 procedures)			during procedure) 0.35% (1/827) (3hr after discharge)		
Barbi 2006[25]	LA/TA/Atropine/ Propofol	Upper gastrointestinal endoscopy procedures	<1 to <10y: 65% (463/716) 10y to <21y: 35% (253/716)	811 procedures in 716 children				Total: 0.7% (6/811 procedures) [3 of these required bag-valve-mask: 0.4% (3/811)]			0.25% (2/811)	7% (58/811 procedures)	VERY LOW
Vespasiano 2007[226], USA	Propofol/LA	MRI, CT, nuclear medicine, lumbar puncture, intrathecal chemotherapy, bone marrow aspirates, electroencephalogram, evoked potentials, hearing tests	Overall age range: 0 mo to 21y 0 to 1mo: 0.4% (29/7304) 1mo to 1y: 1.9% (139/7304) 1 tp 5y: 56% (4076/7304) >5y: 42% (3060/7304)	7, 304	0.01% (1/7304)	0.96% (70/304) (oral airway) 1.57% (115/7304) (nasal trumpet)	0.03% (2/7304)	0.37% (27/7304) (bag and mask)	0% (cardiac arrest)			4.6% (338/7304)	VERY LOW
Larsen 2009[135]	IV propofol					0.04% (2/4716) (mask)	0.02% (1/4716)	0.02% (1/4716)((bag-valve)					VERY LOW

Cravero 2009[46], USA	Propofol used as the sole or primary sedative in 49,836 sedations/anaesthesia encounters: -20.4% (10149/49836) used in addition to: Midazolam [7.5% (3766/49 836)], Ketamine [1.76% (879/49, 836)], Chloral hydrate [0.3% (139/49 836)], Opioids ALL TYPES [10% (5061/49836)], OTHER [0.61% (304/49, 836)] -79.6% (39687/49836) for the remaining encounters	51, 483 primary diagnoses including: neurological (37.2%), haematology/oncology (23.6%), gastrointestinal (11.7%), infectious (5.2%), renal (4.4), orthopaedic (3.9%) congenital heart disease (2.4%), other defined diagnoses (10.6%) other not defined diagnoses (3.9%) no data (0.14%)	0 months to 8 years: 71% (35396/49836) > 8 years: 29% (14440/49836)	49, 836 sedation encounters	N=4 rate: 0.9	Airway obstruction: N=432, rate: 93.2 Emergency airway consultation (does not applied to cases delivered by anaesthesiologists): N=7, rate: 1.5	(cardiac arrest) N=2 rate: 0.4		(during sedation) N=49 rate: 10.6	N=716 rate: 154.4	VERY LOW Indirect population Difficult to draw conclusions as unclear whether sedation used for sedation or anaesthesia and unclear dose
					Reported rates per 10, 000 Inadequate anaesthesia: N=392, rate: 85						

6.9.3 Evidence statements for propofol

6.9.3.1 RCT efficacy and safety for propofol

COMBINATION COMPARISONS

IV propofol + propofol maintenance + local anaesthesia vs. IV midazolam + IV ketamine + IV fentanyl

Vardi 2002[221]

- All patients completed the procedure [low quality evidence]

Compared with children receiving intravenous midazolam + intravenous ketamine + intravenous fentanyl, children receiving intravenous propofol + propofol maintenance + local anaesthesia had significantly:

- Faster recovery time (minutes) [low quality evidence]
- Better satisfaction at sedation period (Ramsay scale) [very low quality evidence]

There was no significant difference in:

- Duration of procedure (minutes) [low quality evidence]
- Satisfaction at induction period (Ramsay scale) [very low quality evidence]
- Assisted ventilation (bag-mask) [very low quality evidence]
- Endotracheal intubation [very low quality evidence]

6.9.3.2 Non RCT safety (adverse events) for propofol

For the characteristics of studies and outcome data on propofol refer to Table 68 and Table 69

- Two studies reported rates of aspiration: from 0% to 0.01%[26,226]
- Four studies reported rates of oral-pharyngeal airway intervention: from 0% to 3%[26,135,168,226]
- Four studies reported rates of endotracheal intubation: from 0% to 0.03%[26,135,168,226]
- Six studies reported rates of assisted ventilation - either bag-valve mask or controlled: from 0% to 0.8%[24-26,135,168,226]
- Two studies reported rates of External cardiac massage: there were no events of cardiac[226] or cardiopulmonary[26] arrest

- Three studies reported rates of vomiting: from 0% to 1.05%[24,25,168].
- Four studies reported rates of oxygen desaturation <90%: from 0% to 7%[26, 24,25,226]

In one study[46] it was unclear whether sedation was used for sedation or anaesthesia and how much dose of the propofol was administered. Based on a total of 49, 836 sedations/anaesthesia encounters, the study reported a range of complications with rates (per 10,000) including:

- Aspiration: rate 0.9 (n=4)
- Airway obstruction: rate 93.2 (n=432)
- Emergency airway consultation (does not apply to cases delivered by anaesthesiologists): rate 1.5 (n=7)
- Cardiac arrest: rate 0.4 (n=2)
- Vomiting during sedation: rate 10.6 (n=49)
- Oxygen desaturation <90%: rate 154.4 (n=716)
- Inadequate anaesthesia: rate: 85, (n=392)

6.9.4 GDG discussion of the evidence for propofol

Propofol, being a short acting intravenous anaesthetic agent, can be titrated to achieve any target level of sedation and anaesthesia. In the evidence examined the success rate of propofol was not always specifically stated but was assumed by the GDG to be 100%. The true level of sedation was often not stated. The GDG appreciated that the difference between sedative and anaesthesia doses was small and that unintentional anaesthesia was a risk with this drug. The GDG agreed that doses above 3mg/kg are likely to cause unconsciousness indistinguishable from anaesthesia. It was noted that doses necessary to cause sedation may depend upon the procedure. For example the dose required for a painless procedure would be less than for a painful procedure. The GDG noted that the dose of propofol required for a painful procedure maybe reduced by the use of analgesia and in this respect the combination of an opioid with propofol may reduce the doses of both drugs.

Seven studies[24-26,168,221,226] were considered by the GDG (very low level evidence). The studies involved procedures ranging from painless imaging, painful ED procedures and endoscopy. The target sedation level was deep or not stated. The GDG considered the doses used and agreed that many of the children would have been anesthetised at some stage.

The safety of propofol was discussed. In one large case series[26] the incidence of oxygen desaturation was 7% and the need for an airway device was approximately 3%. The GDG agreed that tracheal intubation would occasionally be required and that propofol should only be used by teams who had adequate training to manage anaesthesia.

The GDG noted that propofol was used in two studies[24,25] for children undergoing endoscopy. Propofol was being used without any airway device and the GDG agreed that practitioners would need special training to ensure that the airway was not obstructed by the insertion of the endoscope. The GDG believed that laryngospasm was an appreciable risk during this procedure and that sedation teams would need the skills and judgement to manage it.

The GDG discussed the use of a technique combining propofol with other sedation drugs such as midazolam, ketamine and opioids. The GDG understood that combinations of these drugs are being used to provide sedation for dental procedures in the UK. No RCTs were found testing the combinations of these drugs and therefore the efficacy could not be assessed.

The GDG thought that such a technique could cause unintentional deep and prolonged sedation. While it is true that the effects of opioid and midazolam can be reversed by naloxone and flumazenil, the reversal requires prompt administration and sedation may outlast the effects of reversal agent(s).

In contrast to drug combinations, the GDG agreed that unconsciousness and airway effects are more likely with propofol, but are brief. Recovery of full consciousness after propofol is much more rapid and airway obstruction or apnoea can be managed with appropriate skills and equipment.

The GDG discussed the potential economic advantages of using propofol to either sedate or anaesthetise children for a wide variety of procedures. In comparison with almost any other method of sedation, propofol was the most effective apart from ketamine and sevoflurane. Provided intravenous access could be achieved propofol had the advantages of speedy onset and recovery. Propofol could enable a faster turnover of patients than many techniques. The disadvantage however is that propofol would need the same staff and facilities as an anaesthetic. This clearly has resource implications but the GDG agreed that if the demand of procedure was high the rapid nature of propofol sedation/anaesthesia could prove to be economically advantageous

The agreement by the GDG is that economic analysis should be conducted only for sedation techniques commonly available in the NHS. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). Propofol combined with fentanyl was felt to be a strategy commonly used in short painful procedures, and there is some evidence from the systematic review of opioids that propofol plus fentanyl is an effective and safe strategy. The GDG therefore agreed that the combination strategy should be compared to other relevant strategies in the economic analysis conducted for this population group. Details of the considerations of cost-effectiveness with respect to using propofol plus fentanyl in short painful procedures are given in section 6.12.1.2.

6.10 Opioids

Matrix of opioids comparators

Key:

Chloral hydrate = CH
Fentanyl = F
Isoflurane = I
Ketamine=K
Local anaesthesia = LA
Midazolam = M
Nitrous oxide = N_20
Nitrous oxide and oxygen = N_20+02
Opioids = O
Propofol= P
Sevoflurane = S
Triclofos sodium = TS

Opioids vs			
	Reference	**Tables**	**Evidence statements page**
Placebo			
Nil			
Head to head			
Nil			
Combinations			
F + P vs. P + placebo	Cechvala 2008[38] Hollman 2008[94]	Table 70	311
F + P vs. P	Disma 2005[56]	Table 71	311
F + P vs. M + P	Disma 2005[56]	Table 72	312
F + M vs. M + K	Lucas da Silva 2007[151] Kennedy 1998[129]	Table 73	312
F + P vs. P + K	Tosun 2007[215]	Table 74	313
Safety			
RCTs			
Assisted ventilation	Cechvala 2008[38] Hollman 2008[94] Disma 2005[56]	Table 76 Table 76	314

	Kennedy 1998[129]		
ET intubation	Cechvala 2008[38] Hollman 2008[94]	Table 76 Table 76	314
CPR / defibrillation	Lucas da Silva 2007[151]	Table 76 Table 76	314
Desaturation	Cechvala 2008[38] Hollman 2008[94] Disma 2005[56] Lucas da Silva 2007[151] Kennedy 1998[129] Tosun 2007[215]	Table 76 Table 76	314
Vomiting	Cechvala 2008[38] Hollman 2008[94] Kennedy 1998[129] Tosun 2007[215]	Table 76 Table 76	314
Aspiration	Kennedy 1998[129]	Table 76 Table 76	314
Observational studies	Pitetti 2003[184] Sanborn 2005[198] Roback 2005[191] Mamula 2007[157] Sacchetti 2007[197]	Table 76 Table 76	314
Route of administration			
Nil			
Dose			
Nil			

6.10.1 Clinical methodological introduction for opioids

CLINICAL QUESTIONS:

For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, is intravenous morphine, intravenous fentanyl or intranasal diamorphine (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?

- Safe for sedation (at mild, moderate, and deep levels) in different settings?

The literature was searched for systematic reviews and RCTs for the clinical efficacy of opioids (intravenous morphine, intravenous fentanyl or intranasal diamorphine). The search was expanded to include non RCT observational studies for the safety of opioids.

There were no systematic reviews identified for the use of opioids in paediatric sedation.

Five RCTs comparing intravenous morphine, intravenous fentanyl, and intranasal diamorphine with other sedative drugs were assessed for efficacy and safety.

Five non RCT observational studies with total n=2439 were assessed for safety of opioids.

Crossover trials were treated separately from parallel armed trials unless there was sufficient data to allow their combination.

Meta-analyses for RCTs were performed where drug interventions and comparisons and outcomes were sufficiently homogenous and studies were combined regardless of dose, duration of intervention, procedure (within painful and non-painful groups), setting (e.g. dentistry, accident and emergencies) and age.

6.10.2 Evidence profiles for opioids

6.10.2.1 RCT evidence profiles for efficacy and safety for opioids

Study characteristics and methodological quality of the study are provided in Appendix D. GRADE tables for quality assessment of study outcomes and summary of findings are provided below.

COMBINATION COMPARISONS

Table 70: Intravenous fentanyl + intravenous propofol vs. intravenous propofol + placebo; Cechvala, 2008; Hollman 2008[38,94]

Question: Should intravenous fentanyl plus intravenous propofol vs. intravenous propofol plus placebo be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: hospital outpatients
Bibliography: Cechvala 2008[38]; Hollman 2008[94] (Lumbar puncture)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous fentanyl plus intravenous propofol	intravenous propofol plus placebo	Relative (95% CI)	Absolute		
Completion of procedure												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/22 (100%)	22/22 (0%)	not estimable	-	MODERATE	
Anxiety recorded by the study investigator using a validated scale (modified Yale Preoperative Anxiety Scale (mYPAS))												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/22 (0%)[3]	0/22 (0%)	-	not pooled	MODERATE	
Recovery based on the paediatric discharge criteria modified from the Connecticut Children's Medical Centre Scoring System and consisted of two recovery phases: 1) between procedure and when patient ready for discharge and 2) discharge of patients from sedation program after satisfactory completion of phase 2 monitoring criteria; Better indicated by less)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[4]	none	22	22	-	MD -12.50 (-22.4 to -2.6)[5]	MODERATE	
Parents preference												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[6]	none	16/21 (76.2%)	5/21 (23.8%)	RR 3.20 (1.44 to 7.13)[7]	524 more per 1000 (from 105 more to 1000 more) 0 more per 1,000	MODERATE	
Adverse events: Assisted ventilation (flow inflating anaesthesia bag)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious	none	1/22 (4.5%)	1/22 (4.5%)	RR 1 (0.07 to 15)[8]	0 fewer per 1000 (from 42 fewer to 630 more) 0 fewer per 1,000	LOW	
Adverse events: Endotracheal intubation												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2,9]	none	0/22 (0%)[9]	0/22 (0%)	not pooled	-	MODERATE	

Adverse events: Oxygen desaturation <90%											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2,10,11]	none	0/22 (0%)	1/22 (0%)	RR 0.33 (0.01 to 7.76)[10]	0 fewer per 1,000	LOW	
Adverse events: Vomiting											
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	very serious[2,10,11]	none	0/22 (0%)	1/22 (4.5%)	RR 0.33 (0.01 to 7.76)	30 fewer per 1000 (from 45 fewer to 304 more) 0 fewer per 1,000	LOW	

[1] Cechvala 2008[38] (Hollman 2008[94]): double blind study - patients and outcome assessors blinded, ITT - yes, all patients followed and adequate allocation concealment; small study
[2] Cechvala 2008[38]: small study
[3] Cechvala 2008[38]: stated that patients were not statistically different between groups in the level of anxiety as assessed by the mYPAS scale either before or after the administration of fentanyl and placebo
[4] Cechvala 2008[38]: imprecise, confidence intervals cross left confidence limit
[5] Cechvala 2008[38]: p=0.01
[6] Cechvala 2008[38]: imprecise, outside (right) confidence limits; small study
[7] Cechvala 2008[38]: p=0.004
[8] Cechvala 2008[38]: p=1.00
[9] Cechvala 2008[38]: stated there were no events of endotracheal intubation
[10] Cechvala 2008[38]: p=0.49
[11] Cechvala 2008[38]: very wide confidence intervals crossing both confidence limits

Table 71: Intravenous fentanyl + intravenous propofol vs. intravenous propofol; Disma 2005[56]

Question: Should intravenous fentanyl plus intravenous propofol vs. intravenous propofol (with topical and local anaesthesia in both arms) be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Disma 2005[56] (Endoscopy)

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous fentanyl plus intravenous propofol plus topical anaesthesia plus local anaesthesia	intravenous propofol plus topical anaesthesia plus local anaesthesia	Relative (95% CI)	Absolute	Quality	Importance
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/82 (100%)	80/80 (100%)	not estimable	-	MODERATE	
Duration of procedure (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	82	80	-	MD -0.60 (-1.37 to 0.17)[3]	LOW	
Recovery assessed using a validated scale: from completion of scan to achievement of Aldrete score of >=8 (measured with: Aldrete score; range of scores: 1-10; Better indicated by more)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	82	80	-	MD 2.40 (-0.09 to 4.89)[5]	LOW	
Adverse events: Assisted ventilation (bag mask)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[6,7]	none	2/82 (2.4%)	3/80 (3.8%)	RR 0.09 (0 to 1.58)[8]	35 fewer per 1000 (from 38 fewer to 22 more) 0 fewer per 1,000	VERY LOW	
Adverse events: Oxygen desaturation <90%												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	2/82 (2.4%)	3/80 (3.8%)	RR 0.65 (0.11 to 3.79)[9]	13 fewer per 1000 (from 34 fewer to 106 more) 0 fewer per 1,000	LOW	

[1] Disma 2005[56]: ITT appeared to be performed and there were no loss of follow up reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear; small study
[2] Disma 2005[56]: imprecise, crosses left confidence limit
[3] Disma 2005[56]: p=0.13

[4] Disma 2005[56]: imprecise, crosses right confidence limit
[5] Disma 2005[56]: p=0.06
[6] Disma 2005[56]: very imprecise, crosses both confidence limits and very wide confidence interval
[7] Disma 2005[56]: small study
[8] Disma 2005[56]: p=0.10
[9] Disma 2005[56]: p=0.63

Table 72: Intravenous fentanyl + intravenous propofol vs. intravenous midazolam + intravenous propofol; Disma 2005[56]

Question: Should intravenous fentanyl plus intravenous propofol vs. intravenous midazolam plus intravenous propofol (with topical anaesthesia in both arms) be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Disma 2005[56] (Endoscopy)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous fentanyl plus intravenous propofol plus topical anaesthesia	intravenous midazolam plus intravenous propofol plus topical anaesthesia	Relative (95% CI)	Absolute		
Duration of procedure (Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	82	78	-	MD -0.40 (-1.17 to 0.37)[3]	MODERATE	
Recovery assessed using a validated scale: from completion of scan to achievement of Aldrete score of >=8 (measured with: Aldrete score; range of scores: 1-10; Better indicated by more)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	82	78	-	MD -0.10 (-2.46 to 2.26)[5]	MODERATE	
Completion of procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/82 (100%)	78/78 (100%)	not estimable	-	MODERATE	
Adverse Events: Assisted ventilation (bag mask)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/82 (0%)[8]	0/78 (0%)	not pooled	-	MODERATE	
Adverse Events: Oxygen desaturation <90%												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/82 (2.4%)	2/78 (2.6%)	RR 0.95 (0.14 to 6.59)[7]	1 fewer per 1000 (from 22 fewer to 145 more) 0 fewer per 1,000	VERY LOW	

[1] Disma 2005[56]: ITT appeared to be performed and there were no loss of follow up reported; however, allocation concealment and blinding of patients were not stated and blinding of outcome assessors was not clear; small study
[2] Disma 2005[56]: precise, within confidence limits
[3] Disma 2005[56]: p=0.31
[4] Disma 2005[56]: precise within confidence limits
[5] Disma 2005[56]: p=0.93
[6] Disma 2005[56]: very imprecise, crosses both confidence limits and too wide confidence intervals
[7] Disma 2005[56]: p=0.96

[8] Disma 2005[56]:The study reported that no patients needed bag-mask ventilation for assisted ventilation

Table 73: Intravenous fentanyl + intravenous midazolam vs. intravenous midazolam + intravenous ketamine Lucas da Silva 2007[151] and Kennedy 1998[129]

Question: Should intravenous fentanyl plus intravenous midazolam vs. intravenous midazolam plus intravenous ketamine be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: hospital inpatients and accidents and emergencies
Bibliography: Lucas Da Silva 2007[151] (central venous catheter insertion) - hospital inpatients; Kennedy 1998[129] (orthopaedic: fracture or joint reduction) - accidents and emergencies

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous fentanyl plus intravenous midazolam	intravenous midazolam plus intravenous ketamine	Relative (95% CI)	Absolute		
Completion of procedure (Lucas Da Silva 2007[151]; Kennedy 1998[129]) (follow-up mean 101-121 minutes[1])												
2	randomised trial	very serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/158 (98.1%)	158/159 (99.4%)	RR 0.98 (0.95 to 1.01)[4]	20 fewer per 1000 (from 50 fewer to 10 more) 0 fewer per 1,000	LOW	
Induction time (Lucas Da Silva 2007[151]): time from initial sedative administration to onset of the procedure (follow-up mean 7.5 minutes; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	28	29	-	MD 2 (-0.002 to 5.998)[6]	LOW	
Recovery time (Lucas Da Silva 2007[151]): time from end of procedure to awakening (follow-up mean 20 minutes; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	28	29	-	MD -5 (-15 to 7.9)[7]	LOW	
Total time (Lucas Da Silva 2007[151]): time from initial sedative administration to spontaneous eye opening (follow-up mean 101 minutes; Better indicated by less)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	28	29	-	MD 6.5 (-19 to 33)[8]	LOW	
Adverse events: External cardiac massage/defibrillation (Lucas Da Silva 2007[151])												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[9]	none	0/28 (0%)	0/29 (0%)	not pooled	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1,000	LOW	
Adverse events: Oxygen desaturation <90% (Lucas Da Silva 2007[151]) (follow-up 101 minutes)												
1	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[10]	none	0/28 (0%)	2/29 (6.9%)	RR 0.21 (0.01 to 4.13)	55 fewer per 1000 (from 68 fewer to 216 more) 0 fewer per 1,000	LOW	

Induction time (Kennedy 1998[129]): between first midazolam dose and first orthopaedic manipulation (follow-up mean 13 minutes; measured with: time in minutes between first midazolam dose and first orthopaedic manipulation; Better indicated by less)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[11]	none	130	130	-	MD 0.30 (-2.5 to 3.1)[12]	LOW	
Distress during procedure assessed by observer using a validated scale (Kennedy 1998[129]) (measured with: Observational Scale of Behavioural Distress-Revised (OSBD-R); range of scores: 0-23.5; Better indicated by less)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[13]	none	130	130	-	MD 1.62 (1.2 to 2.04)[14]	LOW	
Anxiety during procedure assessed by parent using a validated scale (Kennedy 1998[129]) (measured with: Visual Analogue Scale; range of scores: 0-10; Better indicated by less)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[15]	none	130	130	-	MD 1.01 (0.22 to 1.8)[16]	LOW	
Pain during procedure assessed by parent using a validated scale (Kennedy 1998[129]) (measured with: Visual Analogue Scale; range of scores: 0-10; Better indicated by less)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[15]	none	130	130	-	MD 1.34 (0.53 to 2.15)[17]	LOW	
Total time (Kennedy 1998[129]): from administration of intervention to when patient has been transferred to recovery area (follow-up mean 127.6 minutes[18]; Better indicated by less)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[19]	none	130	130	-	MD -13.90 (-25.46 to -2.34)[20]	LOW	
Adverse events: Aspiration (Kennedy 1998[129]) (follow-up mean 121 minutes; throughout procedure; number of patients)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[21]	none	0/130 (0%)[22]	0/130 (0%)	not pooled	-	LOW	
Adverse events: Assisted ventilation - bag-valve mask (Kennedy 1998[129]) (follow-up mean 121 minutes; throughout procedure)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	very serious[23]	none	0/130 (0%)	2/130 (1.5%)	RR 0.20 (0.01 to 4.13)[24]	12 fewer per 1000 (from 15 fewer to 47 more) 0 fewer per 1,000	VERY LOW	
Adverse events: Vomiting during procedure (Kennedy 1998[129]) (follow-up mean 121 minutes; throughout procedure)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[11,25]	none	0/130 (0%)	1/130 (0.8%)	RR 0.33 (0.01 to 8.11)[26]	5 fewer per 1000 (from 8 fewer to 57 more) 0 fewer per 1,000	LOW	
Adverse events: Vomiting during recovery (Kennedy 1998[129])												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[11]	none	0/130 (0%)	1/130 (0.8%)	RR 0.27 (0.08 to 0.96)[27]	6 fewer per 1000 (from 0 fewer to 7 fewer) 0 fewer per 1,000	LOW	
Adverse events: Oxygen desaturation <90% Kennedy1998[129] (follow-up mean 121 minutes; throughout procedure)												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[11,25]	none	31/130 (23.8%)	8/130 (6.2%)	RR 3.88 (1.85 to 8.11)[28]	179 more per 1000 (from 53 more to 441 more) 0 more per 1,000	LOW	

[1] Lucas Da Silva 2007[151]: mean follow up 101 minutes; Kennedy 1998: mean follow up 121 minutes
[2] Lucas Da Silva 2007[151]: double blinding was deemed impractical because of different dosing algorithms of the drugs used and because medications used present clinically distinguishable effects; small study
[3] Kennedy 1998[129]; quasi randomised; subjects stratified according to initial parental choice to remain in the room or not during reduction and were then randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine; not fully blinded: blinding of patients and parents not stated, two trained observers blinded to study purpose and design reviewed the videotape of each study but unable to blind sedators; ITT performed and all patients followed
[4] Kennedy 1998[129] and Lucas Da Silva: p=0.31
[5] Lucas Da Silva 2007[151]: median results were reported for the outcomes of induction time, total time and recovery time thus not possible to combine with Kennedy 1998[129]; small sample size
[6] Lucas Da Silva 2007[151]: p=0.03; stated median results with p-values on the study
[7] Lucas Da Silva 2007[151]: p=0.40; stated median results with p-values on the study
[8] Lucas Da Silva 2007[151]: p=0.67; stated median results with p-values on the study
[9] Lucas Da Silva 2007[151]: study stated there was an increase in cardiac arrest but 'no intervention was required' and 'no cardiac abnormalities were detected'
[10] Lucas Da Silva 2007[151]: wide confidence intervals crossing both precision limits
[11] Kennedy 1998[129]: small sample size
[12] Kennedy 1998[129]: p=0.83
[13] Kennedy 1998[129]: precise but OBSD-R may be biased by subjectivity of observer
[14] Kennedy 1998[129]: p < 0.00001
[15] Kennedy 1998[129]: crosses right precision limit
[16] Kennedy 1998[129]: p=0.01
[17] Kennedy 1998[129]: p=0.001
[18] Kennedy 1998[129]: control group had the longest total time 127.6 minutes (SD56.2) compared to 113.7 minutes (SD36.9) in the intervention group
[19] Kennedy 1998[129]: crosses left precision limit
[20] Kennedy 1998[129]: p=0.02
[21] Kennedy 1998[129]: small sample
[22] Kennedy 1998[129]: study stated there were no events of aspiration
[23] Kennedy 1998[129]: crosses both precision limits; too wide confidence intervals
[24] Kennedy 1998[129]: p=0.30
[25] Kennedy 1998[129]: precise; wide confidence intervals; no possible to combine with Lucas Da Silva 2007 due to significant heterogeneity (I2=72%; p=0.06) between studies for this outcome
[26] Kennedy 1998[129]: p=0.50
[27] Kennedy 1998[129]: p=0.04
[28] Kennedy 1998[129]: p=0.0003

Table 74: Intravenous fentanyl + intravenous propofol vs. intravenous propofol + intravenous ketamine; Tosun 2007[215]

Question: Should intravenous fentanyl plus intravenous propofol vs. intravenous propofol plus intravenous ketamine (with topical anaesthesia in both arms) be used in children and young people undergoing diagnostic and therapeutic procedures?
Settings: gastroenterology
Bibliography: Tosun 2007[215] (upper and lower endoscopy)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous fentanyl plus intravenous propofol plus topical anaesthesia	intravenous propofol plus intravenous ketamine plus topical anaesthesia	Relative (95% CI)	Absolute		
Completion of procedure (follow-up mean 116 minutes)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/44 (100%)	46/46 (100%)	RR 1 (0 to 0)	0 fewer per 1000 (from 1000 fewer to 1000 fewer) 0 fewer per 1,000	MODERATE	
Duration of procedure (follow-up mean 116 minutes; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	44	46	-	MD -0.20 (-1.27 to 0.87)	MODERATE	
Pain: number of patients who needed additional propofol during induction as evidenced by discomfort/moving during procedure (follow-up 0-1 minute after induction)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/44 (50%)	8/46 (17.4%)	RR 2.88 (1.43 to 5.76)[4]	0 more per 1,000	LOW	
Pain: number of patients who needed additional propofol as evidenced by discomfort/moving during procedure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	41/44 (93.2%)	32/46 (69.6%)	RR 1.34 (1.09 to 1.65)[5]	0 more per 1,000	LOW	
Recovery: time from completion of procedure to recovery/discharge criteria being met (follow-up mean 4.5 minutes; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	46	-	MD 0.80 (-11.16 to 12.76)[6]	LOW	
Adverse events: Oxygen desaturation <90% (follow-up mean 116 minutes; throughout procedure)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	4/44 (9.1%)	3/46 (6.5%)	RR 1.39 (0.33 to 5.88)[8]	25 more per 1000 (from 44 fewer to 317 more) 0 more per	LOW	

										1,000		
Adverse events: Vomiting (follow-up mean 116 minutes; throughout procedure)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	0/44 (0%)	7/46 (15.2%)	RR 0.07 (0 to 1.18)[10]	0 fewer per 1,000	LOW	

[1] Tosun 2007[215]: Unclear allocation concealment; small trial, total n=90;no loss to follow up; double blind
[2] Tosun 2007[215]: precise within precision limits; wide confidence intervals
[3] Tosun 2007[215]: wide confidence interval; few events
[4] Tosun 2007[215]: p=0.003
[5] Tosun 2007[215]: p=0.006
[6] Tosun 2007[215]: p=0.90
[7] Tosun 2007[215]: imprecise, crosses both confidence limits; wide confidence intervals
[8] Tosun 2007[215]: p=0.65
[9] Tosun 2007[215]: imprecise, crosses left confidence limit
[10] Tosun 2007[215]: p=0.07

6.10.2.2 Non RCT evidence profiles for safety for opioids

Five non RCT observational studies in 2,439 patients assessed the safety of opioids[157,184,191,197,198]. There were four prospective studies, and one retrospective study conducted for the following procedures: imaging procedures (1), accidents and emergencies procedures (3) as well for GI procedures (1).

The non RCT study characteristics for opioids are presented in Table 76.

The non RCT adverse event table for opioids is presented in Table 76.

Table 75: Opioids Non RCT Study Characteristics Safety Review

Study	Setting	ASA	Sedation type	Gender, % male	Drug (doses)	Fasting
Pitetti 2003[184], USA	Accidents and emergencies Prospective descriptive study	81% were Class I; 17% were class II; 1.3% were class III and 0.1% were class IV.	Procedural sedation	65.1% boys in total sample (791)	IV fentanyl citrate + midazolam & IV morphine sulphate + midazolam and IV midazolam Mean fentanyl dose: 2.7 mcg /kg Midazolam 0.1 mg/kg; Morphine not stated	Mean fasting 5.0 + 2.8 hours before sedation.
Sanborn 2005[198], USA	Imaging Retrospective chart review	44% of total subjects were ASA I; 51% ASA ii; 4% ASA III; 0.1% ASA IV; 0.1% ASA V.	IV fentanyl + midazolam and IV fentanyl	56% of total were male	Doses not stated	Not stated
Roback 2005[191], USA	Accidents and emergencies Prospective observational database	Not stated	Procedural sedation	60.4% of total were male	Midazolam + fentanyl vs. midazolam alone	Not stated
Mamula 2007[157], USA	Operating Room	ASA I-III	Intravenous or general anaesthesia	55% (674/1226)	IV midazolam (2 mg/2mL) & fentanyl (100 mcg/2mL) during 1 minute. Midazolam 0.05 to 0.1 mg/kg max 2 mg; fentanyl 1 mcg/kg max 75 mcg Oral midazolam for anxious patients; IV diphenhydramine as additional sedative	3 hours
Sacchetti 2007[197], USA	Accidents and emergencies Prospective observational database	94.1%of total cohort Class I, 5.3% class II and 0.6% class III.	Procedural sedation	Not stated	Fentanyl & Morphine	Not stated

Table 76: Opioids Safety: Non RCTs

Study type, reference, country	Drug / Comparison	Procedure	Age	Total N	ADVERSE EVENTS, rate: % (n)								GRADE PROFILE
					Aspiration				Cardiac arrest requiring either/or		vomiting	oxygen desaturation <90%	EVIDENCE QUALITY
						oral-pharyngeal airway	endotracheal intubation	assisted ventilation	external cardiac massage	defibrillation			
Pitetti 2003[184], USA	IV fentanyl citrate + midazolam hydrochloride Vs. midazolam alone	A & E	0-21 years	686 vs 65 Complications reported as total adverse events: 23.5% vs. 1.5%									VERY LOW
	IV morphine sulphate + midazolam Vs. IV midazolam	A & E	0-21 years	48 vs. 65 Complications reported as total adverse events: 16.7% vs. 1.5%									VERY LOW
Sanborn 2005[198], USA	Fentanyl	MR and Ct imaging	Mean age of total sample was 4.8 years + 4.6	42/16467	0	0	0	0	0	0		0	VERY LOW
Roback 2005[191], USA	Midazolam +Fentanyl Vs. Midazolam	A & E	19 days to 32 years; median 6.7 years	336 vs. 260				All patients experiencing apnea or laryngospasm were managed with administrati			Midazolam/ fentanyl 1.8% (6/336) Midazolam 0.8% (2/260)	Respiratory adverse events reported and included oxygen saturation	VERY LOW

								on of oxygen, breathing cues, airway positioning or bag-mask ventilation. Numbers of each intervention were not provided.				<90%, apnea or laryngospasm Midazolam/ fentanyl 19.3% (65/336) Midazolam 5.8% (15/260)	
Mamula, 2007[157], USA	iv midazolam/fentanyl/ only when needed: oral Mid for anxious children & diphenhydramine to reach desired effect	oesophagogastro duodenoscopies colonoscopies and combined	range: 0.1-34 y 4%(55/1226) were ≥18 years median: 10 y mean: 9.05 y (SD 5.8)	1226	0% (pulmonary aspiration)		0%	0.16% (2/1226) (bag/mask ventilation)	0% (0/1226) (cardiac arrest)		5.2% (64/1226) (during recovery)		VERY LOW
Sacchetti 2007[197], USA	Fentanyl	A & E	0-20 years	51/977 *episode of apnea with fentanyl and etomidate which required reversal was only adverse event reported.									VERY LOW

6.10.3 Evidence statements for opioids

6.10.3.1 RCT efficacy and safety for opioids

COMBINATIONS COMPARISONS

IV fentanyl + IV propofol vs. IV propofol + placebo

Cechvala 2008[38]; Hollman 2008[94]

- All patients completed the procedure [moderate quality evidence]

Compared to intravenous propofol + placebo, the intravenous fentanyl + intravenous propofol group was significantly:

- Preferred among parents [moderate quality evidence]
- Faster in recovery time (Connecticut Children's Medical Centre Scoring System) [moderate quality evidence]

There were no events of:

- Endotracheal intubation [moderate quality evidence]

There was no significant difference in:

- Anxiety (mYPAS) [moderate quality evidence]
- Assisted ventilation (flow inflating anaesthesia bag) [low quality evidence]
- Oxygen desaturation < 90% [low quality evidence]
- Vomiting [low quality evidence]

IV fentanyl + IV propofol vs. IV propofol

Disma 2005[56]

- All patients completed the procedure [moderate quality evidence]
- There was no significant difference in:
- Recovery time (Aldrete score) [low quality evidence]
- Duration of procedure [low quality evidence]
- Oxygen desaturation <90% [low quality evidence]
- Assisted ventilation (bag-mask ventilation) [very low quality evidence]

IV fentanyl + IV propofol vs. IV midazolam + IV propofol

Disma 2005[56]

- All patients completed the procedure [moderate quality evidence]

There was no significant difference in:

- Duration of procedure [moderate quality evidence]
- Recovery time [moderate quality evidence]
- Oxygen desaturation <90% [very low quality evidence]

There were no events of:

- Assisted ventilation (bag mask) [moderate quality evidence]

IV fentanyl + IV midazolam vs. IV midazolam + IV ketamine

For the outcome of oxygen desaturation (<90%), we found evidence of highly significant heterogeneity (I^2=72%; p=0.06) between two RCTs[129,151]. Possible sources of heterogeneity could be attributed to the differences between the studies in procedure performed (catheter insertion versus orthopaedic fracture or joint reduction) and length of procedure (orthopaedic fracture or joint reduction takes longer), setting (inpatients versus accidents and emergencies) and varying dose of combination agents. We therefore felt it was not appropriate to pool the RCTs together in a meta-analysis and the studies are presented separately for this outcome.

Lucas da Silva 2007[151], *Kennedy 1998*[129]

There was no significant difference in:

- Completion of the procedure [low quality evidence]

Lucas da Silva 2007[151]

There was no significant difference in:

- Induction time [low quality evidence]
- Recovery time (minutes) [low quality evidence]
- Total sedation time (minutes) [low quality evidence]
- Oxygen desaturation <90% [low quality evidence]

There were no events of:

- External cardiac massage or defibrillation [low quality evidence]

Kennedy 1998[129]

Compared to the intravenous midazolam + intravenous ketamine group, the intravenous midazolam + intravenous fentanyl group had significantly:

- Higher distress scores during procedure (OSBD-R) [low quality evidence]
- Higher anxiety scores (VAS) [low quality evidence]
- Higher pain scores during procedure (VAS) [low quality evidence]
- Shorter total time [low quality evidence]
- More oxygen desaturation <90% [low quality evidence]
- Less vomiting during recovery [low quality evidence]

There were no events of:

- Aspiration [low quality evidence]

There was no significant difference in:

- Completion of procedure [low quality evidence]
- Induction time [low quality evidence]
- Vomiting during procedure [low quality evidence]
- Assisted ventilation (valve-mask) [very low quality evidence]

IV fentanyl + IV propofol vs. IV propofol + IV ketamine

Tosun 2007[215]

- All patients completed the procedure [moderate quality evidence]

Compared with intravenous propofol + intravenous ketamine + topical anaesthesia, children who received intravenous fentanyl + intravenous propofol + topical anaesthesia had significantly:

- More pain (number of patients) in the first minute after induction [low quality evidence]
- More pain (number of patients) during procedure [low quality evidence]

There was no significant difference in:

- Length/duration of procedure [moderate quality evidence]
- Recovery time [low quality evidence]

- Oxygen desaturation <90% [low quality evidence]
- Vomiting [low quality evidence]

6.10.3.2 Non RCT safety (adverse events) for opioids

For the characteristics of studies and outcome data refer to Table 76 and Table 76.

- One study reported a 1.6% rate of assisted ventilation[157].One study reported no events[198]. No other reports of respiratory intervention were elicited from the studies.
- There were no cardiac events reported in five studies.
- Vomiting rates were reported in two studies of midazolam + fentanyl: 1.8%[191] and 5.2%[157].
- Adverse respiratory events including oxygen saturation <90%, apnea and laryngospasm were reported with the use of midazolam + fentanyl at 19.3% vs midazolam alone at 5.8%[191]. One study reported no events[198]. No other reports of desaturation were elicited from the studies.

6.10.4 GDG discussion of the evidence for opioids

The GDG found no studies that opioids (morphine, fentanyl and diamorphine) were effective for any diagnostic or therapeutic procedure when used alone to cause sedation rather than simply analgesia. In the studies found, opioids were always combined with other drugs and the GDG agreed that they had been used for their analgesic properties within a sedation technique. The sedative potential of these selected opioids could not be determined from the evidence.

There were no studies on diamorphine.

There was one RCT[184] of morphine in which it was combined with midazolam in the Emergency department setting. The efficacy of this combination could not be determined from the data because the evidence level was very low. The GDG agreed that morphine was a drug that had an analgesic action that was much longer than most painful procedures and for this reason shorter acting opioids such as fentanyl were likely to be more suitable.

All other evidence on opioids was provided from studies of combinations of fentanyl with either midazolam or propofol. Most studies were in the emergency department setting but one was in a hospital in children undergoing lumbar puncture. The GDG agreed that the principles of sedation for painful procedures in the ED were applicable to sedation for similar painful procedures in other settings.

The choice of opioid to be used in combination with midazolam was debated. In the early discussions of the GDG it was agreed that evidence for pethidine would not be sought because it had a longer action than fentanyl and because it was not widely used.

The combination of fentanyl with midazolam was used with the intention of maintaining moderate sedation but the GDG appreciated that it was sometimes difficult to titrate the drugs to provide sedation and analgesia to overcome the pain of the procedure without causing deep sedation or appreciable suppression of airway reflexes or breathing. The hazard of opioid induced respiratory depression occurring after the procedure had been completed was noted by the GDG. In one study[191] of children undergoing procedure in the ED setting, desaturation, apnoea or laryngospasm was reported as occurring in up to 19% of children. In comparison, ketamine has a safer record and has a similar induction and recovery time. The GDG agreed that even with careful titration of fentanyl and midazolam, deep sedation and airway obstruction or apnoea are possible and that this combination should only be used by a trained sedation team. Airway management skills and equipment are essential for this drug combination.

Fentanyl combined with propofol was considered by the GDG to be a useful deep sedation or anaesthesia technique. Two RCTs[38,56] were considered. One showed that the addition of fentanyl to propofol reduced recovery time and the other found that propofol doses could be reduced. Fentanyl was associated with fewer adverse events.

The general principle agreed by the GDG is that only sedation techniques commonly available in the NHS should be included in the economic analysis. Economic analysis was conducted for six broad groups (dental procedure in children, dental procedure in adolescents, short painful procedures, painless imaging, oesophago-gastroscopy and colonoscopy). A combination of fentanyl and midazolam was felt to be commonly used in colonoscopy and short painful procedures (for example, reduction of a dislocated joint), whereas fentanyl plus propofol was felt to be commonly used in short painful procedures. There is some evidence that these combination strategies are effective and well tolerated. The GDG therefore agreed that they should be included in the economic analysis. Details of the considerations of cost-effectiveness with respect to using fentanyl plus propofol in short painful procedures, and using fentanyl plus midazolam in colonoscopy are given in section 6.12.1.2 and 6.12.3.2 respectively.

6.11 SEDATION SPARING

6.11.1 Clinical methodological introduction

CLINICAL 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?

The literature was searched for systematic reviews and RCTs for sedation sparing i.e. how much of the sedation drug is used in each arm alone or in combination with pharmacological intervention.

There were no systematic reviews, RCTs or observational studies that reported relevant outcome measures for analyses of our efficacy and safety outcomes.

6.11.2 Evidence statements

There were no RCTs or observational studies relevant for analyses of our efficacy and safety outcomes.

The GDG felt that sedation sparing techniques are not among the sedation techniques commonly used in the NHS, and decided that an economic analysis should not be done for these techniques.

6.12 CLINICAL SETTINGS

There are different types of diagnostic and therapeutic procedures. For example, some procedures are painful yet others are painless but require prolonged immobility. The efficacy and safety of sedation depends therefore not only on the drug or technique but also on the procedure itself. After reviewing the drugs, the GDG sought to group the evidence according to the type of procedure to enable the development of guidance on effective and well tolerated sedation for specific procedures. There are many types of procedures and the GDG accepted that guidance on each and every procedure was not practicable. For the purposes of this guidance, the GDG used the classifications of

- painless imaging
- painful procedures
- dental procedures
- endoscopy

which they believe cover the majority (more than 90%) of common procedures.

Guidance for uncommon procedures can be obtained by applying relevant principles from the guidance below. Before considering sedation for a procedure the practitioner will need to understand what the procedure entails, what is expected of the patient, and what the sedation technique needs to achieve (see chapter 4).

6.12.1 Painless imaging

Many children will be able to tolerate painless diagnostic imaging tests without sedation drugs. Adequate patient preparation, parental involvement, and a child-friendly environment are important for success (see section 4.3 Psychological preparation). Non-pharmacological methods such as play therapy and distraction techniques may be also helpful for children who are able to co-operate. The majority of children of school age will manage well with these techniques as an alternative to sedation. Highly anxious children may be helped by having anxiolytic drugs. However there are a large number of children who are too ill, in pain or have behavioural problems that prevent them lying still for prolonged imaging.

The target level of sedation will vary according to the imaging procedure. CT scans and echocardiography can be done under moderate sedation. Some children may need to be asleep in order to tolerate complex or prolonged investigations. Examples include MRI and nuclear medicine imaging that may involve the child keeping still for up to an hour. MRI can be particularly frightening because it is noisy and involves lying still in an enclosed space. The level of sedation achieved while the patient is asleep is uncertain; they may be moderately sedated and sleeping naturally, be deeply sedated or be anaesthetised. Determining the level of sedation relies on stimulating the patient which may spoil the image.

Ideally "wide margin of safety" drugs cause the patient to sleep and be either moderately or deeply sedated. Not all children will sleep with these drugs. Anaesthesia, by comparison is always effective and short acting. Low doses of anaesthetic agents also cause sedation of uncertain depth however the true depth may be estimated from the drug dose.

6.12.1.1 Summary of evidence in painless imaging

The GDG extracted essential evidence from each drug review and incorporated this evidence into Table 77 and Table 78 below. The tabular presentation was developed as a way to summarise disparate data, ranging across various drug types, drug combinations, specialty areas and procedural techniques. The tables have thus been organised by setting and include the following: painless procedures (imaging), dentistry, painful procedures and GI procedures. The primary efficacy outcome was completion of procedure.

On the basis of the evidence, the GDG made a decision regarding the efficacy and safety (benefits and harms) of each drug and drug combination reviewed. They indicated their decision in the tables below.

Table 77: GDG judgment on drugs safety and efficacy in painless procedures

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety (judged by the GDG)	Evidence level	Ref
CH vs. GA	oral	80 mg/kg to max of 2 g	Not stated	CT	Favours GA. Effective	NR	Low	Thompson 1982*[213]
High dose CH for CT	oral	100 mg/kg in a single dose with maximum of 2 grams	Mean age 2.18 years	CT	(Non-RCT)	1 aspiration (severe mental retardation) 2 ETT due to obstruction by tongue (1 profound retardation) 4.3% vomiting. Well tolerated for ASA 1-2	Prospective cohort, N=326 ? Low	Greenberg Faerber, & Aspinall 1991 [83]
High dose CH for MRI	oral	100 mg/kg	Not stated	MRI	(Non-RCT)	Vomiting 4%. Well tolerated	Prospective cohort, N=300 ? Low	Greenberg, 1993[84]
CH sedation for diagnostic imaging	oral	64 + 13 mg/kg chloral hydrate	Not stated	MRI	(Non-RCT)	GI side-effects. Well tolerated	Prospective cohort N=336 Low	Malviya 2000[156]
CH: Intermediate vs. high dose	oral	70 mg/kg vs. 100 mg/kg	Mean: 38 + 31 months	MRI	NS for completion of procedure; induction favours high dose. Effective	Well tolerated	Moderate	Marti-Bonmati 1995*[159]
CH for effective and well tolerated sedation	oral	Chloral hydrate syrup 68 +/- 1mg/kg	Mean age 41 + 30 months	MRI	(Non-RCT)	Vomiting 6.9%. Well tolerated	Prospective cohort N=596 Low	Ronchera-Oms 1994[194]
CH Sedation of neurologically impaired children for MRI	oral	50 – 100 mg/kg to a maximum dose of 1.5 g/kg	Mean age 28.2 + 18.1 months	MRI	(Non-RCT)	0.2% vomiting, 0.5% SpO2<90%. Well tolerated	Retrospective cohort N=888 (Neuro impaired)	Cortellazzi 2007[43]
CH vs. music therapy*	oral	60 mg/kg with	1 month -5	EEG	Favours music	NR	Low	Loewy

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety (judged by the GDG)	Evidence level	Ref
		max of 1.5 g	years		therapy. Effective			2005[150]
CH for effective and well tolerated sedation	oral	Median dose of chloral hydrate was 77 mg/kg	3 weeks to 14 years; median age 13 months	Echocardiography	(Non-RCT)	Vomiting 6% Drop in SpO2>5% baseline in 6% (children with heart disease) Not well tolerated for children with heart disease	Prospective cohort N>400	Napoli, Ingall, & Martin 1996[171]
CH for sedation for echocardiography	oral	Oral chloral hydrate (80 mg/kg, maximum 1 g)	Birth to 64 months	Echocardiography	(Non-RCT)			Heistein 2006[92]
High dose CH for ophthalmic examination	oral	80-100 mg/kg chloral hydrate not to exceed 3 g.	1 month - 5 years	Ophthalmic examination	(Non-RCT)	No vomiting or desaturation. Well tolerated	Prospective cohort N=302	Fox 1990[69]
P/LA	IV	PRO rarely: 2 mg/kg PRO maint 1-2 mg/kg PRO cont infusion initiated at 150 mcg/kg/min LA: at discretion of intensivist	Overall range: 0 mo to 21y	MRI, CT, nuclear medicine, lumbar puncture, intratechal chemotherapy, bone marrow aspirates, electroencephalogram, evoked potentials, hearing tests	Not reported	Well tolerated	Very low	Vespasiano 2007[226]

Table 78: GDG judgment on combination drugs safety and efficacy in painless procedures

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
IV F + M and IV F	IV	Not stated	Mean age of total sample was 4.8 years + 4.6	Imaging		No adverse outcomes observed	Very low	Sanborn 2005[198]
P/O_2 CH/O_2	IV	PRO: 2 mg/kg after iv access + dilute PRO infusion at a rate of 80-140 mcg/kg/min CH: children <1 y 75 mg/kg (max 2g)	Overall: <1 mo to 17y PRO range: <1 mo-to 17y CH range: <1 mo to 7 y	Scans of the head, thorax, abdomen, pelvis and spine	Not reported	Well tolerated	Very low	Merola 1995[168]
S+ $N_2$0	inhal	1.8-2% sevoflurane; 50% N20	1 day-12 months	MRI	Effective	Well tolerated	Low	De Sanctis Briggs 2005[51]

6.12.1.2 Cost-effectiveness for painless imaging

The economic evidence for this group was obtained by modelling the treatment pathway for high dose chloral hydrate and comparing this with general anaesthesia (see Appendix F on cost-effectiveness analysis). This was informed by evidence from clinical and safety review as well as GDG expert opinion. High dose chloral hydrate was more costly than general anaesthesia because this type of sedation was assumed to be less successful but also to require the same staff levels as general anaesthesia.

In cases where the addition of a sedationist physician is required, as with chloral hydrate, sedation could still be cost saving compared to general anaesthesia but this will depend primarily on:

- The exact success rate: as the success rate gets lower, the cost of a sedation strategy increases. The GDG reported that very high rates of success (above 95%) are achievable with all techniques if patients are selected carefully.

- 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.

6.12.1.3 Evidence to recommendations for painless imaging

Of all the imaging techniques MRI is the most common scenario in which sedation may be needed. MRI usually lasts between 30 and 60 minutes and CT imaging is much shorter. To be still enough, the patient usually needs to be sleeping, and the true target level of sedation is uncertain; it may be moderate, deep or anaesthesia. The GDG agreed that the ideal sedation method should not cause sedation much longer than the scan itself. For this reason, techniques such as propofol or sevoflurane have advantages of fast induction time, certainty of completion, and rapid recovery. Many children presenting for imaging are uncooperative because they are young, they have a behavioural problem or because they are distressed or in pain. A further advantage of propofol or sevofluorane is that they can be used in all age groups and all types of patients.

Infants who sleep after a feed may lie still enough without any sedation. Also, many children can be calmed sufficiently and persuaded to lie still without the use of sedation. Occasionally an anxiolytic drug may help them but only if they are cooperative. Children who are uncooperative need sedation or anaesthesia. The GDG considered that sedation with Chloral hydrate was an effective and well tolerated alternative to anaesthesia but only in children less than 15kg. The success rate of chloral hydrate may be maximised by careful patient assessment and selection. The GDG recognised that chloral hydrate may not always be effective and that intravenous midazolam is a drug commonly used to either increase the depth of sedation or prolong sedation.

Chloral hydrate causes sleep lasting approximately one hour and is therefore less appropriate for scans lasting a few minutes. An advantage of chloral is that it does not require the services of an anaesthesia team. The GDG recognised that chloral hydrate may not always be effective and that intravenous midazolam is a drug commonly used to either increase the depth of sedation or prolong sedation.

Midazolam was shown to be one of the most cost-effective sedation techniques for dental procedures (6.12.3.2) and the GDG believe this may well be the case for painless imaging as well.

Other types of painless imaging such as trans-thoracic echocardiography or EEG do not require the child to be completely immobile and they may therefore be managed with minimal or moderate sedation. Anaesthesia would not be appropriate for these investigations either because the risks outweigh the benefits in patients with cardiac problems or, in the case of EEG, anaesthesia may suppress the EEG signal under investigation.

6.12.1.4 Recommendations on painless imaging

Recommendation 28	Do not routinely use ketamine[‡‡‡‡], [§§§§]or opioids[*****] for painless imaging procedures.

Recommendation 29	For children and young people who are unable to tolerate a painless procedure (for example during diagnostic imaging) consider one of the following drugs, which have a wide margin of safety: - chloral hydrate[†††††] for children under 15 kg - midazolam[‡‡‡‡‡].

[‡‡‡‡] Ketamine is a dissociative agent: the state of dissociative sedation cannot be readily categorised as either moderate or deep sedation; the drug is considered to have a wide margin of safety

[§§§§] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs

[*****] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs

[†††††] Chloral hydrate is used in UK clinical practice for sedating children and young people for painless procedures. At the time of publication (December 2010) chloral hydrate did not have UK marketing authorisation for this indication. See appendix J.

[‡‡‡‡‡] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.

Recommendation 30	For children and young people who are unable to tolerate painless imaging with the above drugs, consider one of the following, used in specialist techniques, which have a narrow margin of safety (see section on personnel and training): - propofol[§§§§§] - sevoflurane[******].

[§§§§§] Propofol is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) propofol did not have UK marketing authorisation for this age group. See appendix J.

[******] Sevoflurane is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) sevoflurane did not have UK marketing authorisation for this indication. See appendix J.

6.12.2 Painful Procedures

Many children undergo brief painful procedures following injury (such as suture of lacerations and orthopaedic manipulations in emergency departments). In a recent review[19] the prompt administration of analgesia has been promoted not only because it is important and compassionate, but because it can reduce anxiety and increase cooperation of the child or young person to enable the procedure to be carried out with sedation rather than anaesthesia. Recently the term "procedural sedation and analgesia" has been used because it emphasizes that the analgesia component of sedation is crucial.[131] Many painful procedures can be carried out under local anaesthesia, provided the child or young person is cooperative. If the patient is unable to cooperate local anaesthesia is still important because the dose of sedative drug can be minimized if the patient has no pain. The following recommendations in this section are applicable to any painful procedure not only in the emergency setting but elsewhere such as a hospital ward.

There are several potentially useful sedation techniques for painful procedures. The decision to undertake a particular technique should be influenced by factors such as the type and duration of a painful procedure, the age and developmental stage of the child, and the urgency of a painful procedure. In particular, clinicians should consider the target depth of sedation required, and the relative requirement for analgesia, sedation, immobility and amnesia. Prolonged or complex procedures should be carried out under general anaesthesia.

The sedation techniques recommended for painful procedures are considered in relation to the three target levels of sedation although it should be appreciated that there is variation in the sedation level achieved. Ketamine induces sedation which has different characteristics to any other sedation drug. Ketamine causes 'dissociative sedation' which is a trance-like cataleptic state, with profound analgesia, sedation, amnesia, and immobility. Ketamine tends to preserve airway reflexes, spontaneous respiration, and cardiovascular stability. Nevertheless occasionally ketamine can cause airway complications including laryngospasm. Dissociative sedation has been included in the category of deep sedation because the training and facilities needed for safe practice are similar (see sections 4.4 Personnel and training and 4.5 Clinical environment and monitoring). However ketamine is considered to have a wider margin of safety than other anaesthetic agents, although practitioners must be able to manage the potential complication of laryngospasm; after an initial normal blood pressure measurement, repeat blood pressure measurements are generally required only if other vital signs are abnormal (and otherwise may be intrusive particularly when using sub-dissociative doses)

Wound suture and foreign body removal are common examples of painful procedures usually carried out under minimal sedation. Moderate sedation is required for brief emergency orthopaedic procedures such as transferring a child with a fractured limb or placing the limb into a splint and reduction of a dislocated joint. Titration of the drugs used to achieve moderate sedation is important to avoid excessive respiratory depression. Examples of procedures usually carried out under dissociative or deep sedation are suture of lacerations to the face and nail bed in young children, and orthopaedic manipulations.

In an urgent or emergency situation the time of the last food and drink intake in children and young people is often uncertain. Moreover, trauma may delay gastric emptying. The problem of whether to use sedation (or anaesthesia) within a few hours after admission to hospital in a patient who may not be fasted is common. In most situations the procedure can be delayed although there will be practical problems of arranging for the procedure later. The risk of pulmonary aspiration during deep sedation and anaesthesia will need to be balanced with the risk of delaying the procedure. In many situations it may be reasonable to use a sedation technique with a wide margin of safety in a patient who is not fasted (see section 4.2 Fasting).

Some of the sedation drugs are anaesthetic agents such as ketamine and propofol, and their use by 'non-anaesthetists' has been controversial. This has arisen because anaesthesia services are not always available. Skills necessary for safe sedation can be achieved by practitioners who are not fully trained anaesthetists (see section 4.4 Personnel and training).

6.12.2.1 Summary of evidence in painful procedures

The GDG extracted essential evidence from each drug review and incorporated this evidence into Table 79 and Table 80 below. The tabular presentation was developed as a way to summarise disparate data, ranging across various drug types, drug combinations, specialty areas and procedural techniques. The tables have thus been organised by setting and include the following: painless procedures (imaging), dentistry, painful procedures and GI procedures. The primary efficacy outcome was completion of procedure.

On the basis of the evidence, the GDG considered the efficacy and safety (benefits and harms) of each drug and drug combination reviewed. They indicated their decision for each drug in the tables below.

Table 79: GDG judgment on drugs safety and efficacy in painful procedures

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
70% N20	Inhaled	70%	0-18 years	Emergency procedures	N/A	Vomiting 4.7% (26/548); 0.18% (1/548) desaturation	Non RCT	Babl 2008[22]
50% N20	Inhaled	50%	0-18 years	Emergency procedures	N/A	Vomiting 3.9% (4/101); 0% (1/548) desaturation	Non RCT	Babl 2008[22]
50% N20	Inhaled	50%	<19 years	Mixed procedures including emergency, GI, radiology, lumbar puncture, etc.	N/A	'Minor events' 5% (375/7511) and 0.3% 'major' events (25/7511)	Non RCT	Gall 2001[73]
50% N20	Inhaled	50%	2 studies in systematic review with mean ages of 3.7 years and 10 years.	Laceration repair and fracture reduction	N/A	No reported vomiting or desaturation. Well tolerated	Non RCT	Faddy 2005[61]
K IV vs IM	IV vs. IM		4mo-18y	Orthopaedic reduction	Favours IV for distress score but longer total time for IM. Effective.	Desat: IV 9/109 vs IM 4/99; vomiting: IV 13/109 vs IM 26/99; ventilation: IV 2/109	Low quality	Roback 2006[192]
Ketamine	IM		0-15y	Emergency procedures miscellaneous	N/A	0.4% (5/1022) bag mask ventilation; desaturation 0.9% (9/1022); vomiting 6.7% (68/1022)	Non RCT	Green 1998[81], Green 1998[82]
Ketamine	IM		Not stated	Suturing, minor surgery in A & E	N/A	17% vomiting in recovery or at home (85/501); 0.5% desaturation; 15% mild recovery agitation (71/501); 3% moderate agitation (16/501); 0.8% pronounced agitation (4/501)	Non RCT	McGlone 2004[163]

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
Ketamine	Not stated		0-20 years	Minor trauma including laceration repair, fracture care, lumbar puncture, radiology etc.	N/A	No reported adverse events	Non RCT	Sachetti 2007[197]
IV F/IV P vs IV P/Placebo	IV	Fenta: 1 mcg/kg PRO: 1-2 mg/kg/min infusion	2-17 y	Lumbar puncture	Effective	Well tolerated	Low quality	Cechvala 2008[38]
IV F IV M vs IV M/IV K	IV	Mid: 0.15 mg/kg (max:0.5 mg/kg) Fenta: 1 mcg/kg (max 100 mg) Keta: 0.5 mg/kg	3 mo-14 y	Intravenous line placement	Effective	Well tolerated	Low quality	Lucas Da Silva 2007[151]
P/O analgesics (either Mo or F)	IV	PRO: initial dose 1mg/kg (max 40 mg); supplemental doses 0.5 mg/kg (max 20 mg) Morphine: 0.1 mg/kg (max 5 mg) Fentanyl: 1-2 mcg/kg (max 50 mg)	Overall: 1-18y Median : 8 y	Fractures, dislocations, examination of ocular burn	Not reported	Well tolerated	Very low quality	Bassett 2003[26]
Oral M vs. Placebo	Oral	0.5 mg/kg	oral M 7.7 y (SD4.4) placebo 7.9 y (SD4.4)	IV insertion	All completed procedure (effective.) and insufficient data (NSD) for procedure duration and recovery (not effective)	Not reported	Moderate	Liacouras1998[140]

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
IN M vs. Placebo	IN	0.4 mg/kg	median 2.5 y (range: 0.75-4.9)	Suture/laceration repair	Yes, favours M in patient satisfaction. Effective.	Vomiting: no events. Well tolerated	Very low - low	Theroux 1993[212]
IN M vs. Placebo	IN	0.2 mg/kg	mean age: 5 y (range: 0.8-18 y)	Needle insertion	Insufficient data for pain scores assessed by either patient (NSD) or parents (favours M) (not effective) Favours M for parents satisfaction (Effective) and NSD for patient satisfaction (Effective)	Not reported	Very low - low	Ljungman 2000[149]
Oral M vs. Placebo	Oral	0.5 mg/kg	mean age 4.1 y (range: 2-6)	Suture/laceration repair	Yes, NSD in completion of procedure (Effective.)	no events of aspiration, cardio-respiratory or cardiac massage. Well tolerated	Moderate	Luhman 2001[152]
Oral M vs. Placebo	Oral	0.3 mg/kg	mean age 4.8 y (SD3) (range 0.8-10)	Suture/laceration repair	Yes, favours M for distress score (Effective.) and NSD for anxiety (Effective.)	Not reported	Moderate	Fatovich 1995[63]
Rectal M/Non-pharma* vs. N2O/Non-pharma	R	0.35-0.5 mg/kg	mean age: RM 8:7 y (SD4:9), N2O 8:6 (SD3:8)	spasticity injections -cerebral palsy-	No, it is reported to favour N2O group for anxiety (p=0.010) (Not effective.)	NSD in vomiting. Well tolerated	Moderate	Zier 2008[239]

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
					Yes, for parents satisfaction, it is reported NSD between groups (p=0.10) (Effective.) No, insufficient data for total time, it is reported NSD between groups (Not effective.)			
IV M/IV Mo vs. IVPRO/IV Mo / LA	IV	0.1 mg/kg	(range 2-18 y) mean age: IVM 8.6 y (SD4.2) PRO 9 y (SD3.8)	Reduction of fractures	Yes, all completed, and NSD for induction and procedure time and for pain (Effective.) No, favours PRO group for recovery and total time (Not effective.)	No events for aspiration, external cardiac massage or assisted ventilation. Well tolerated Selective reporting for O2 desat. Not well tolerated	Very low-low	Havel 1999[91]
Oral M vs. IN M	Oral vs. IN	0.5 mg/kg vs. 0.25 mg/kg	(range: 2 -10 y) mean age: Oral M 4.4 y (SD2.5) IN M 3.5 y (SD2)	Suture/laceration repair	Yes, all completed the procedure and NSD for total time (Effective.)	NSD for total time. Well tolerated	Very low - moderate	Connors 1994[42]
Oral M vs. IN M	Oral vs. IN	1 mg/kg vs. 0.4 mg/kg	(range 1 to 5 y)	Suture/laceration repair	Yes, favours oral M for distress score and NSD for total time	Selective reporting for vomiting. Not well tolerated	Very low	Everitt 2002[60]

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
					(Effective.)			
Rectal M: 2mg vs. 1mg	R 2mg/kg vs. 1mg/kg	2mg/kg vs. 1 mg/kg	(range 0.5-4) higher dose: 2.5(SD1), lower dose: 2.13(SD0.9).	Suture/laceration repair	Yes, NSD in satisfaction, recovery time and total time (Effective.)	No cardio-respiratory events. Well tolerated Selective reporting in vomiting. Not well tolerated	Low - moderate	Kanegaye 2003[124]

Table 80: GDG judgment on combination drugs safety and efficacy in painful procedures

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
M/K vs M/F	IV		5-15	All completed* go back to paper and check	Yes (Effective) Favours M/K pain, distress, anxiety)	More desat in M/F; more vomiting in M/K; assisted ventilation in 2 M/K pts	Low quality	Kennedy 1998[129]
IV P/F vs IV M/K	IV		3-18	All completed	Yes (Effective) Favours M/K (pain, distress, anxiety) but longer recovery time	KM: 4/54 desat; P/F 18/59 desat; vomiting KM 2/54; recovery/agitation 3/54	Low quality	Godambe 2003[77]
M/K vs IV M/Axillary block	IV		=>8y	All completed	Yes (Effective), NSD for pain and distress scores	N/A	Low quality	Kriwanek 2006[132]
M/K vs haematoma block/entonox	IV		5-17y	All completed	Yes (Effective) NSD for pain distress but longer recovery time for K/M	Vomiting: K/M 24/55 vs N2O 26/47	Low quality	Luhmann 2006[153]
M/K vs IN M	IV vs. IN		6 mo-12y	Suturing or painless: all completed	Yes (Effective) shorter induction time for Ketamine and longer total time for Mid/K	K/M: 1/27 desat; 2/27 vomiting IN M: 1/26 vomiting	Low quality	Acworth 2001[10]
K (with M in 31% of cases)	IV		0-15y	Emergency procedures miscellaneous	N/A	Desat: 1/156; bag/mask: 1/156; vomiting: 6/156 (1 during sedation; 5 after); recovery agitation: mild 2/156	Non RCT	Green 1998[81] Green 1998[82]
K vs. K / M	IV ket	Not stated	39 days to 22 years	Fracture reduction; laceration repair; lumbar puncture; imaging; dental	N/A	Desat and laryngospasm: 6.1% (91/1492)	Non RCT	Roback 2005[191]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
	IV Ket/ Midaz.	Not stated	4.8 months to 18 years		N/A	Desat and laryngospasm: 10% (30/299)	Non RCT	
K/M vs. F/M	IV		3/12 – 15 years-	Insertion CVC	Yes (Effective)	Yes (Well tolerated)	Non RCT	Lucas Da Silva 2007[151]
M/F vs. M Procedural sedation	IV	Not stated	19 days to 32 years; median 6.7 years	A & E	N/A	Respiratory adverse events reported and included oxygen saturation <90%, apnea or laryngospasm Midazolam/ fentanyl 19.3% (65/336) Midazolam 5.8% (15/260) ;vomiting - Midazolam/ fentanyl 1.8% (6/336) Midazolam 0.8% (2/260)	Non RCT	Roback 2005[191]
IV F/M vs. M Procedural sedation	IV	Mean fentanyl dose: 2.7 mcg /kg Midazolam 0.1 mg/kg;	0-21 years	A & E	N/A	686 vs 65 Complications reported as total adverse events: 23.5% vs. 1.5%	Non RCT	Pitetti 2003[184]
IV Mo/M vs. IV M Procedural sedation	IV	Midazolam 0.1 mg/kg Morphine dose not stated	0-21 years	A & E	N/A	48 vs. 65 Complications reported as total adverse events: 16.7% vs. 1.5%	Non RCT	Pitetti 2003[184]
IVP/LA vs. IV M/IV K/IV F	IV	PRO: initial: 2.5	overall: 7.3 y (SD5.7)	Intraarticular steroid injection, bronchoscopy,	Yes (Effective)	Yes (Well tolerated) with appropriate	Very low	Vardi 2002[221]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
		mg/kg in children, 3 mg/kg in infants; maint: 200 mcg/kg/min Lidocaine: 0.1 mL M: 0.1 mg/kg Keta: 2mg/kg Fenta: 2mcg/kg	PRO 7.5 y (SD5.7) Mid/Keta/Fenta 6.93 y (SD5.8)	bone marrow aspiration/biopsy, trans-oesophageal echocardiography, PEG/Gastroscopy, Other		training		
IV P/O analgesics (either Mo or F)		PRO: initial dose 1mg/kg (max 40 mg); supplemental doses 0.5 mg/kg (max 20 mg) Morphine: 0.1 mg/kg (max 5 mg) Fentanyl: 1-2 mcg/kg (max 50 mg)	Overall: 1-18y Median : 8 y	Fractures, dislocations, examination of ocular burn	Not reported	Yes (Well tolerated)	Very low	Bassett 2003[26]
Oral M/N_2O vs. Placebo/N_2O	Oral	0.5 mg/kg	mean age 4.1 y (range: 2-6)	Suture/laceration repair	Yes (Effective) all completed the procure	Yes (Well tolerated) no events of aspiration, cardio-respiratory and NSD in vomiting	Low-moderate	Luhmann 2001[152]
IV M/IV K vs. IV K/Placebo	IV	0.1 mg/kg	(range 2-14 y) mean age: IV M/IVKeta 7.1 y (SD3.9) IV Keta 6.0 y (SD3.5)	Lumbar puncture	Yes (Effective) favours Mid group for induction time and for parents satisfaction it is also reported as	No (Not well tolerated) favours Keta/Placebo for O2 desat (Not well tolerated)	Low	Dilli 2008[55]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
					significant (p=0.001), NSD for recovery time			
IV M/IV K vs. IV K	IV	0.05 mg/kg	(range 1-15 y) mean age (IQR range) IV M/Keta 7 y (4-11) IV Keta 6 y (2-11)	IV Catheter insertion	Yes (Effective) all completed the procedure	Quite well tolerated, no events and NSD for assisted ventilation Yes (Well tolerated) Favours Mid/Keta for vomiting No (Not well tolerated) Favours Keta/Placebo for O2 desat	Low - moderate	Sherwin 2000[203]
IV M/IV K vs. IV K	IV	0.1 mg/kg	(range 0.3-18 y) median age (IQ range): IV M/Keta 5.6 y (3.4-9.6) IV Keta 6.8 y (4.4-10.3)	mixed	Yes (Effective) all completed the procedure and NSD for patient satisfaction (Effective) and insufficient data (NSD) for duration of procedure (Not effective)	Quite well tolerated, no events for aspiration or external cardiac massage Yes (Well tolerated) NSD for assisted ventilation Yes (Well tolerated) Favours Mid/Keta for vomiting Favours Keta/Placebo for O2 desat (Red)	Low - moderate	Wathen 2000[229]
IV M/F IM M/K IV M/K IN M/FI	IV, IM, IN, Oral	0.01-0.05 mg/kg	(age range: of 1,188 patients: 1 mo-21 y) median: 48 mo	paediatric emergency department for diagnostic imaging, oral and rectal sedation and analgesia. IM and IV in radiology	N/A	Yes (Well tolerated) Yes, no events endotracheal intubation; low rates for assisted ventilation (0.5% to 0.60%) or vomiting (0.55% to	Non RCT	Peña 1999[180]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
				suite		2.5%) (Well tolerated) Quite safe for O2 desat (ranged 0.60% to 4%)		
IV M/K or IM M/K	IV or IM	0.1 mg/kg	(age range: 19 d-32 y) mean age: 4.9-10.8 y	fracture reduction, laceration repair, lumbar puncture, imaging, other	N/A	Vomiting rate from 0.8% to 10.1%	Non-RCT	Roback 2005[191]

6.12.2.2 Cost-effectiveness for painful procedures

The economic evidence for this group was obtained by modelling the treatment pathway for two sedative drugs (ketamine and a combination of fentanyl plus propofol) and comparing these with general anaesthesia (see Appendix F on cost-effectiveness analysis). This was informed by evidence from clinical and safety review as well as GDG expert opinion.

Sedation drugs were shown to be cost-saving compared to general anaesthesia, and ketamine was less costly than fentanyl plus propofol. However, we would be cautious about concluding that any one sedation technique is the lowest cost for all patients, since in extremely anxious patients minimal to moderate sedation will fail and the cost of a rescheduled procedure will be incurred. Therefore, careful patient selection should lead to a more effective and more cost-effective service.

6.12.2.3 Evidence to recommendations for painful procedures

Management of minor trauma in the ED is the most common scenario for brief painful procedures but the principles of effective and well tolerated sedation in the ED can be applied to other areas such as hospital wards.

The GDG agreed that analgesia and/or local anaesthesia was a crucial component in any sedation technique for a painful procedure. Sedation may be used to make possible injection of local anaesthetic, which in turn may be sedation sparing. If local anaesthesia was not practical or appropriate, analgesia by another method would be necessary. Nitrous oxide is potentially effective for cooperative patients but for many children either an opioid or ketamine would be necessary. Opioids are not effective alone and need to be combined with midazolam or propofol. They should be used with caution because they cause respiratory depression especially after the pain of a procedure has abated. The GDG recognised that it was essential to titrate the dose of opioid and sedative carefully, and adhere to recommended maximum dose, to avoid "overshooting" and causing unintended deep sedation or anaesthesia. Airway obstruction is a potential complication in this situation, and airway management skills are a requirement for the practitioner. Ketamine, in contrast, is effective without any other drug and tends to maintain vital reflexes. Moreover it can be given intramuscularly if venous access is difficult and it is applicable to infants and children. The GDG agreed that ketamine sedation had many advantages and that it was a well tolerated technique provided teams were trained to use it safely and competent to manage potential complications.

The main debate was whether ketamine sedation, delivered by an ED team, would have economic advantages over anaesthesia, delivered by an anaesthesia team the day after the trauma. The GDG considered that this was a common and realistic scenario and that guidance on this issue would help healthcare provider manage resources efficiently. Economic modelling showed ketamine to be lower cost than either propofol or general anaesthesia for forearm fracture. We did not model minimal sedation for this group but for dental procedures either nitrous oxide or midazolam were shown to be the lowest cost sedation techniques (6.12.3.2).

6.12.2.4 Recommendations on painful procedures

Recommendation 31	In children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation), when the target level of sedation is minimal or moderate, consider: - nitrous oxide (in oxygen) and/or - midazolam[††††††] (oral or intranasal)

Recommendation 32	For all children and young people undergoing a painful procedure, consider using a local anaesthetic, as well as a sedative.

Recommendation 33	For children and young people undergoing a painful procedure (for example, suture laceration or orthopaedic manipulation) in whom nitrous oxide (in oxygen) and/or midazolam (oral or intranasal) are unsuitable consider: - ketamine[‡‡‡‡‡‡], [§§§§§§] (intravenous or intramuscular), or - intravenous midazolam[*******] with or without fentanyl[†††††††] (to achieve moderate sedation).

[††††††] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.
[‡‡‡‡‡‡] Ketamine is a dissociative agent: the state of dissociative sedation cannot be readily categorised as either moderate or deep sedation; the drug is considered to have a wide margin of safety.
[§§§§§§] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs
[*******] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.
[†††††††] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.

Recommendation 34	For children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation) in whom ketamine (intravenous or intramuscular) or intravenous midazolam with or without fentanyl (to achieve moderate sedation) are unsuitable, consider a specialist sedation technique such as propofol[‡‡‡‡‡‡‡] with or without fentanyl .

[‡‡‡‡‡‡‡] Propofol is used in UK clinical practice for sedation of children and young people. At the time of publication (December 2010) propofol did not have UK marketing authorisation for this age group. See appendix J.

[§§§§§§§] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.

6.12.3 Dental procedures

The provision of adequate anxiety control is an integral part of the practice of dentistry. The General Dental Council (GDC) has indicated that this is both a right for the patient and a duty placed on the dentist[75]. The GDC also state that for dental treatment under general anaesthesia this should "only be carried out when it is judged to be the most clinically appropriate method of anaesthesia; and only take place in a hospital setting with critical care facilities".

Child dental anxiety is widespread[223]. Many anxious children can be satisfactorily treated using relative analgesia (RA), this combines behaviour management techniques with inhaled nitrous oxide and oxygen. RA is the mainstay of paediatric dental sedation but this approach is unsuccessful in some children[201]. In such cases, control of pain and anxiety poses a significant barrier to dental care and a dental general anaesthetic (DGA) is often seen as the only option. However, DGA carries its own risks and dental treatment provided under DGA also tends to be more radical, with a greater proportion of extractions than fillings[89]. Since 2000 there has been a sea-change in the provision of pain and anxiety management in dentistry in the UK. This has resulted in an increased emphasis on the safe provision of conscious sedation instead of a reliance on general anaesthesia. General anaesthesia should be provided only in response to clinical need. The publication of 'A Conscious Decision' in 2000 resulted in the cessation of general anaesthesia for dentistry in the primary care setting[53]. In 2002, DGA was prohibited in non-hospital settings in England.

The vast majority of dental treatment is carried out in a primary care setting. All children deserve appropriate anxiety control for any dental procedure. The method of anxiety control should be individually selected for each patient. A range of sedation techniques is required; each technique ensuring a wide margin of safety between conscious sedation and the unconscious state provided by general anaesthesia[9,200,208].

In dentistry, standards and guidance for "standard" and "alternative" sedation in the UK have been published by expert working groups[9,200,208]. This NICE guidance both builds on and is consistent with existing guidance for dentistry.

6.12.3.1 Summary of evidence for dental procedures

The GDG extracted essential evidence from each drug review and incorporated this evidence into Table 81 and Table 82 below. The tabular presentation was developed as a way to summarise disparate data, ranging across various drug types, drug combinations, specialty areas and procedural techniques. The tables have thus been organised by setting and include the following: painless procedures (imaging), dentistry, painful procedures and GI procedures. The primary efficacy outcome was completion of procedure.

On the basis of the evidence, the GDG made a decision regarding the efficacy and safety (benefits and harms) of each drug and drug combination reviewed. They indicated their decision in the tables below.

Table 81: GDG judgment on drugs safety and efficacy in dental procedures

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
50% N_2O vs.100% O_2	Inhaled	50%	36-55 months	Dental	NSD in quiet behaviours	Not reported	Low	McCann 1996[161]
40% N_2O/O_2 vs.100% O_2	Inhaled	40%	5-9 years	Dental	Yes (Effective) Distress score favours nitrous oxide	Yes (Well tolerated)	Low	Primosch 1999[187]
Oral M/Non-pharma vs. Placebo/Non-pharma	Oral	0.5 mg/kg	< 4 y	Dental	Yes (Effective) favours M in procedure completion and duration	Not reported	Very low - low	Kapur 2004[125]
Oral M	Oral	0.5 mg/kg; max 10 mg per appt.; mean 8.6 mg/kg	range: 0.9-10.5 y mean: 5.4 y	Dental	N/A	O2 desat: 1.55% (9/579) (Well tolerated)	Non RCT	Hulland 2002[98]
IN M vs. IM M	IN vs. IM	IN& IM M: 0.2 mg/kg	(range: 1-5 y) mean age: IN M: 3.5 y (SD0.7) (range 2.5-5) IM M: 3.4 y (SD 0.6) (range 2-4.5)	Dental	Yes (Effective) favours IN M in induction time and recovery	Yes (Well tolerated), no events for vomiting	Moderate	Shashikiran 2006[202]
IN M vs. IM M	IN vs. IM	IN& IM M: 0.2 mg/kg	(range: 1-5 y) mean age: IN M: 3.5 y (SD0.7) (range 2.5-5) IM M: 3.4 y (SD 0.6) (range 2-4.5)	Dental	Yes (Effective) favours IN M in induction time and recovery	Yes (Well tolerated) no events for vomiting	Moderate	Lee-Kim 2004[138]
CH: High dose vs. low	oral	50 mg/kg vs. 75 mg/kg	Mean: 31	Dental	Favours high dose	Not reported	Low	Houpt

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
dose*			months		Yes, (Effective) wrong technique for procedure????			1985[97]
CH vs. IN M	oral/ IN	62.5 mg/kg CH; 0.2 mg/kg midazolam	Mean: 41.8 months + 11.4 months	Dental	NS but recovery favours midazolam Yes (Effective)	Not reported	Low	Dallman 2001*[49]
CH/hydroxyzine vs M/acetaminophen	oral	50 mg/kg not to exceed 1 g and 25 mg hydroxyzine vs 0.5 mg/kg midazolam with acetaminophen 10 mg/kg	Average 48 months in CH group vs. 42 months in Midazo-lam group	Dental	NSD Yes (Effective)	NR	Moderate	Reeves 1996*[189]
Oral TS vs Oral M	Oral	TRI 70 mg/kg M: 0.5 mg/kg	overall: 3-9 y	dental - mixed: extractions, restorations, pulpotomies, brief	No (Not effective)	Not reported	Very low	Singh 2002[205]

Table 82: GDG judgment on combination drugs safety and efficacy in dental procedures

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
CH + N_2O vs. Placebo + N_2O*	Oral/inhaled	50 mg/kg CH + 50% nitrous oxide vs. placebo + 50% nitrous oxide	19-41 months	Dental	Outcomes not reported (Crying & movement scores suggested chloral more effective, but not uniformly so) Yes (Effective)	Vomiting in 10.5% chloral group, 5% placebo (Well tolerated)	Moderate	Houpt 1989[96]
CH/hydroxyzine and N_2O	Oral/inhaled	Average dose of chloral hydrate 776 mg (55 mg/kg)	Mean age 2.6 years	Dental	(Non-RCT)	Vomiting 8.1% (Well tolerated)	Retrospective, non-RCT Low	Needleman, Joshi, & Griffith, 1995[173]
N_2O vs. Behavioural management	Inhaled	Not stated	Not stated	Dental	Yes (Effective) Anxiety score favours nitrous oxide	Not reported	Very low	Veerkamp 1993[224] & Veerkamp 1995[222]
30% N_2O vs. Transmucosal M	Inhaled	30%	10-16 years	Dental	Yes (Effective)	Yes (Well tolerated)	Low	Wilson 2007[235]
40% N_2O + IV M vs. Medical air + IV M	Inhaled	40%	Mean age 9.5 years	Dental	Yes (Effective) Favours nitrous oxide	Yes (Well tolerated)	Moderate	Averley 2004[20]
40% N_2O + IV M vs. 0.3% S and 40% N_2O + IV M	Inhaled	40%	Mean age 9.6 years	Dental	Favours sevoflurane + nitrous oxide group	Yes (Well tolerated)	Moderate	Averley 2004[20]
0.3% S and 40% N_2O + IV M vs. Medical air +IV M	Inhaled	40%	Mean age 9.1 years	Dental	Yes (Effective) Favours sevoflurane and nitrous oxide	Yes (Well tolerated)	Moderate	Averley 2004[20]
30% N_2O vs. IV M	Inhaled	30%	12-16 years	Dental	Yes (Effective) Favours nitrous oxide	Yes (Well tolerated)	Low	Wilson 2003[231]
30% N_2O/70% O_2 vs. Oral M	Inhaled	30%	10-16 years	Dental	Yes (Effective) Favours nitrous	Yes (Well tolerated)	Low	Wilson 2002 a & b[233,234]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
					oxide			
50% N_2O vs. 50% nitrogen + O_2	Inhaled	50%	1 month – 18 years	Dental	Yes (Effective)	Yes (Well tolerated)	Low	Fauroux 2004[64]
S + N_2O vs. N_2O	inhaled	0.1-0.0.3% sevoflurane; 40% N20	3-10 years mean age: 6.0 y (sevoflurane + N20); 6.2 y (N20)	dental	Yes (Effective)	Yes (Well tolerated)	Moderate	Lahoud 2002[134]
IN M/N_2O (50%) 0.3 mg/kg vs. 0.2 mg/kg	IN 0.3 mg/kg vs. 0.2 mg/kg	0.3 mg/kg	mean age 2.7 y (range: 1.7-3.5)	Dental	Yes (Effective) all completed procedure	Yes (Well tolerated) no events for vomiting	Moderate	Fuks 1994[71]
IN M/ N_2O (30-50%) 0.3 mg/kg vs. 0.2 mg/kg	IN 0.3 mg/kg vs. 0.2 mg/kg	0.3 mg/kg vs. 0.2 mg/kg	(range 5-20) average: higher dose: 0.3-11.6 y lower dose: 0.2-13.6 y	Dental	Yes, NSD in completion of procedure and duration of procedure (Effective)	Yes (Well tolerated), no events for assisted respiration or vomiting after procedure and NSD in O2 desat or vomiting during procedure	Very low – low - moderate	Fukuta 1994[72]
Oral M/N_2O (40%) vs. IN M/N_2O (40%)	Oral vs. IN	Oral M 0.5 mg/kg IN M 0.2 mg/kg	(range 1.5-5.9) mean age: Oral M: 3.3 y IN M: 3.1 y	Dental	Yes, NSD in completion of procedure (Effective)	Yes (Well tolerated), NSD for O2 desat	Very low - low	Hartgraves 1994[90]
Oral M/N_2O 45% vs. IN M/N2O 45%	Oral vs. IN	0.7 mg/kg vs. 0.3 mg/kg	mean age: Oral M 3.4 y (SD11) IN M 3.2 y (SD10)	Dental	Yes (Effective), favours IN M for induction and total time	Not reported	Low - moderate	Lee-Kim 2004[138]

6.12.3.2 Cost-effectiveness for dental procedures

The economic evidence for dental procedures in *children* was obtained by modelling the treatment pathway for a tooth extraction for four sedation drugs evaluated to be well tolerated and efficacious in the previous section. Nitrous oxide plus oxygen, nitrous oxide plus midazolam, sevoflurane plus nitrous oxide, sevoflurane plus nitrous oxide plus midazolam were compared with general anaesthesia (see Appendix F on cost-effectiveness analysis). For *adolescents* we modelled the treatment pathway for a tooth extraction using midazolam compared with general anaesthesia. This was informed by evidence from clinical and safety review as well as GDG expert opinion.

Nitrous oxide plus oxygen with or without iv midazolam were the two least costing strategies for tooth extraction in children. Midazolam was less expensive than general anaesthesia for tooth extraction in adolescents. However, we would be cautious about concluding that any one sedation technique is the lowest cost for all patients, since in extremely anxious patients minimal to moderate sedation will fail and the cost of a rescheduled procedure will be incurred. So careful patient selection should lead to a more effective and more cost-effective service.

In general, the cost of the drugs is less important than the cost of the staff involved. We found that sedation is clearly cost-saving compared to general anaesthesia in cases where the operating dentist is able to administer sedation without the addition of a sedationist dentist, typically for minimal to 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 dentist is required (typically for deeper conscious sedation), sedation could still be cost saving compared with general anaesthesia but this will depend primarily on

- The facility and equipment costs: we have not captured this in our analysis.
- The success rate: As the success rate gets lower, the cost of a sedation strategy increases. The GDG reported that very high rates of success (above 95%) are achievable with all techniques if patients are selected carefully.
- 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.

A published case study has shown that in one district in the North East of England, the charges associated with sedation strategies in primary dental care were likely to be substantially lower than the equivalent charge for the same procedure conducted under GA[101].

6.12.3.3 Evidence to recommendations for dental procedures

The GDG acknowledged the considerable sedation experience of UK dentists. Many children currently require both dental extractions and conservative treatment and many are too anxious to allow the insertion of local anaesthesia. Sedation for dentistry requires that the patient opens their mouth and therefore they need to remain conscious.

Moderate sedation with intravenous midazolam, is considered to be effective for selected children and young people who are cooperative, and younger children who can tolerate a nasal mask can be managed with nitrous oxide.

In the past, if these were not effective, anaesthesia has often been the only alternative. The GDG agreed that additional sedation techniques could be effective for patients who cannot be managed by midazolam or nitrous oxide. If demand is high, alternative sedation techniques would be necessary. The common concern is that additional sedation drugs, especially in combination, may not be predictable enough for widespread use. Sevoflurane and propofol for example may only be safe enough for use by specialist sedation teams.

The GDG agreed that there were potential important economic advantages of avoiding hospital based anaesthesia services. Economic modelling showed midazolam or nitrous oxide to be the lowest cost strategies in suitably selected patients. The training of dental sedation teams was regarded as crucial.

6.12.3.4 Recommendation on dental procedures

Recommendation 35	For a child or young person who cannot tolerate a dental procedure with local anaesthesia alone, to achieve conscious sedation consider: - nitrous oxide and oxygen or - midazolam[********]. If these sedation techniques are not suitable or sufficient, refer to a specialist team for an alternative sedation technique.

[********] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.

6.12.4 Endoscopy

Gastrointestinal (GI) endoscopy procedures are commonly required in children and young people. The procedures consist of upper GI endoscopy (often called oesophago-gastro duodenoscopy [OGD] or gastroscopy) and lower GI endoscopy (colonoscopy). In children and young people the majority of procedures are diagnostic; however, there are some therapeutic techniques performed (for example oesophageal dilatation and polypectomy) that make the procedure more technically difficult and time consuming. Upper endoscopy is uncomfortable but not usually painful. The target level of sedation during upper endoscopy is considered to be no deeper than moderate sedation. The child or young person will need to maintain their airway reflexes for an OGD because vomiting and regurgitation are common. Moreover the endoscope itself may obstruct the airway in an unconscious patient. Colonoscopy may be uncomfortable but can be tolerated by many children and young people under moderate sedation. The use of an analgesic drug is often necessary. If sedation is not successful, anaesthesia should be used and in many centres anaesthesia is the only method used. Nevertheless in a recent survey of members of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition sedation was found to be used in about 30% of units and especially for children of secondary school age and older.

Recently, anaesthesia agents have been used to sedate to the target level that the patient needs in order to tolerate the procedure. This is usually deep sedation but in most cases the patient is anaesthetized albeit for a brief period. Such a method does not necessarily require tracheal intubation and allows effective short acting sedation. Whoever administers anaesthetic agents must be trained to manage the complications of airway obstruction and respiratory depression (see section 4.4 Personnel and training).

6.12.4.1 Summary of evidence in endoscopy

The GDG extracted essential evidence from each drug review and incorporated this evidence into Table 83 and 85 below. The tabular presentation was developed as a way to summarise disparate data, ranging across various drug types, drug combinations, specialty areas and procedural techniques. The tables have thus been organised by setting and include the following: painless procedures (imaging), dentistry, painful procedures and GI procedures. The primary efficacy outcome was completion of procedure.

On the basis of the evidence, the GDG made a decision regarding the efficacy and safety (benefits and harms) of each drug and drug combination reviewed. They indicated their decision in the tables below.

Table 83: GDG judgment on drugs safety and efficacy in endoscopy

DRUG (alone, or with local anaesthesia)	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
IN M vs. Placebo	IN	0.2 mg/kg	age range: 2-12 y	Endoscopy	Yes (Effective) NSD in distress score	Not reported	RCT Mod-low	Fishbein 1997[67]
IV P vs. IV F/IV P	IV	Fentanyl: 1mcg/kg PRO: 3mg/kg TA: Lidocaine larynx and EMLA cream	PRO/Fenta 6.8 y (SD2.8) PRO/TA 6.7 y (2.9)	Endoscopy	Yes (Effective)	Yes (Well tolerated)	low	Disma 2005[56]
P/LA/TA	IV	PRO: mixed according to age/weight LA: 1 to 10 mg TA: EMLA cream	overall <1 to <21y	Upper gastrointestinal endoscopy procedures	Not reported	Yes (Well tolerated)	Very low	Barbi 2006[25]
P/LA/TA	IV	PRO: mixed according to age/weight LA: 1 to 10 mg TA: EMLA cream	overall <1 to <21y	Upper endoscopies, colonoscopies, painful procedures	Not reported	Yes (Well tolerated)	Very low	Barbi 2003[24]

Table 84: GDG judgment on combination drugs safety and efficacy in endoscopy

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
P/K vs P/F	IV	Ket 1mg/kg Prop 1.2mg/kg Fent 1mcg/kg	1-16years	Endoscopy	Yes (Effective)	No (Not well tolerated) Vom 15% ket (0 fent group) p=0.012 Desat no difference (6-9%)	Low-moderate	Tosun 2007[215]
K/M/Me	IV	0.75-2 mg/kg		Endoscopy	N/A	Yes (Well tolerated) 1.2% assisted vent	Non RCT	Gilger 2004[76]
Oral M/IV P vs. IV P	Oral	0.5mg/kg	mean age: Oral M/IV PRO 8 y (SD3) PRO 9 y (SD3)	Endoscopy	No, favours PRO in recovery time No (Not effective) and NSD for duration of procedure Yes (Effective)	Not reported	low - Moderate	Paspatis 2006[178]
IV M/IV P vs. IV P	IV	0.1 mg/kg	(range 1-12 y) mean age: IV M 7.1 y (SD3.1) PRO/Lido 6.7 y (2.9)	Endoscopy	Yes, all completed the procedure and NSD in duration of procedure and recovery time Yes (Effective)	Yes (Well tolerated) NSD in oral-pharyngeal airway and O2 desat	Low - moderate	Disma 2005[56]
IV M/IV Me vs. Placebo/IV Me	IV	0.05-.1 mg/kg (max 2 mg)	(range 2-12 y)	Endoscopy (esophagogastroduodenoscopy)	Yes, NSD in distress score and duration of procedure Yes (Effective)	Not reported	Low - moderate	Fishbein 1997[67]
P/K vs P/F	IV	Ket 1mg/kg Prop 1.2mg/kg Fent 1mcg/kg	1-16years	Endoscopy	Yes (Effective)	No (Not well tolerated) Vom 15% ket (0 fent group) p=0.012 Desat no difference (6-9%)	Low-moderate	Tosun 2007[215]

DRUG COMBINATION	Route	Dose	Age	Procedure	Efficacy	Safety	Evidence level	Ref
M/K (IV 98% or IM)/ 15% Me	IV	Ket 1mg/kg and titrated, median 1.34 mg/kg Dose midaz not known		Endoscopy	N/A	'Amber' 3% bag and mask	Non RCT	Green 2001[80]
K/M/Me	IV	0.75-2 mg/kg		Endoscopy	N/A	Yes (Well tolerated) 1.2% assisted vent	Non RCT	Gilger 2004[76]
IV M/F	IV	0.05-0.1 mg/kg; max 2 mg n.b. oral M to anxious children	(range: 0.1-34 y) median: 10 y mean: 9.05 y (SD 5.8)	Endoscopy (oesophagogastro duodenoscopies colonoscopies and combined)	N/A	Quite well tolerated, no events: aspiration, cardiac arrest, endotracheal intubation 0.16%(2/1226) needed bag/mask ventilation Yes (Well tolerated) 1.2% assisted vent 5.2% (64/1226) vomited during recovery Yes (Well tolerated) 1.2% assisted vent	Non RCT	Mamula 2007[157]
IV F/IV P vs IV M/IV P	IV	Fenta: 1mcg/kg PRO: 3mg/kg Mid: 0.1 mg/kg TA: Lidocaine-larynx and EMLA cream	Fenta/PRO 6.8 y (SD2.8) Mid/PRO 7.1 y (SD3.1)	Endoscopy	Yes (Effective)	Yes (Well tolerated)	Moderate	Disma 2005[56]

* Indicates RCT extracted for efficacy review

6.12.4.2 Cost-effectiveness for endoscopy

The economic evidence for *oesophago-gastroscopy* was obtained by modelling the treatment pathway for midazolam and comparing it with general anaesthesia (see Appendix F on cost-effectiveness analysis). The economic evidence for *colonoscopy* was obtained by also modelling the treatment pathway for midazolam plus fentanyl and comparing this combination with general anaesthesia. This was informed by evidence from clinical and safety review as well as GDG expert opinion.

Midazolam was shown to be less expensive than general anaesthesia in oesophago-gastroscopy, and in colonoscopy, the combination sedation strategy, midazolam plus fentanyl, was less expensive than general anaesthesia. However, we would be cautious about concluding that any one sedation technique is the lowest cost for all patients, since in extremely anxious patients minimal to moderate sedation will fail and the cost of a rescheduled procedure will be incurred. Therefore, careful patient selection should lead to a more effective and more cost-effective service.

6.12.4.3 Evidence to recommendations for endoscopy

Gastroenterological endoscopy is uncomfortable. Gastroscopy requires control of pharyngeal and oesophageal reflexes to overcome retching. Colonoscopy may need opioid analgesia. The GDG felt that a large proportion of children and young people requiring these procedures were old enough to be cooperative and that moderate sedation was effective. It was agreed that deep sedation was potentially hazardous if it was administered by untrained practitioners and without safe resources. The choice of opioid to be used in combination with midazolam combination of midazolam was debated. In the early discussions of the GDG it was agreed that evidence for pethidine would not be sought primarily because it had a longer action than fentanyl but also because it was not widely used. In respect of endoscopy however the GDG was advised by one of its members that pethidine may be in common use for colonoscopy. Pethidine may be safer than fentanyl if practitioners were more familiar with its use because they would be less likely to “overshoot” and cause unconsciousness or respiratory depression. Training in the use of any new technique was considered to be crucial.

It was agreed that moderate sedation may not always be effective enough and that sometimes sedation may have to be abandoned. Patient assessment and selection will be important to minimise sedation failure. Occasionally sedation can become too deep and this results in prolonged recovery.

The GDG agreed that whenever moderate sedation is ineffective a short acting titratable drug such as propofol was ideal. Propofol however readily causes unconsciousness and the hazard of pulmonary aspiration is a special concern with this technique. Staff training and facilities for anaesthesia will be necessary for propofol based techniques. If an anaesthesia team is available either sevoflurane or propofol can be used to induce deep sedation or anaesthesia and this can be applied to children of all ages undergoing procedures of variable length. Tracheal intubation may be needed for gastroscopy and this can be readily achieved by an anaesthesia team.

Economic modelling showed midazolam (with fentanyl in the case of colonoscopy) to be lower cost than general anaesthesia for endoscopy. The GDG agreed that there were potentially important economic advantages of using propofol rather than moderate sedation and that this should be considered by healthcare providers.

6.12.4.4 Recommendations on endoscopy

Recommendation 36	Consider intravenous midazolam[††††††††] to achieve minimal or moderate sedation for upper gastrointestinal endoscopy.

Recommendation 37	Consider fentanyl[‡‡‡‡‡‡‡‡] (or equivalent opioid) in combination with intravenous midazolam to achieve moderate sedation for lower gastrointestinal endoscopy.

[††††††††] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.
[‡‡‡‡‡‡‡‡] At the time of publication (December 2010) the BNFc stipulated that if deep sedation is needed an anaesthetic agent (for example, propofol or ketamine), or a potent opioid (for example, fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs.
[§§§§§§§§] Midazolam is used in UK clinical practice for sedating all children and young people up to the age of 18. At the time of publication (December 2010) midazolam did not have UK marketing authorisation for children younger than 6 months or for oral or buccal administration. See appendix J.

6.13 Research recommendations on drugs for sedation in infants, children and young people

- For children and young people under the age of 19 having minor painful procedures, what potent analgesic drugs can be combined with midazolam to provide safe moderate sedation?

Why it is important

Midazolam has a strong safety profile in inducing either minimal or moderate sedation. For painful procedures midazolam should be combined with analgesia. Ideally analgesia is achieved by local anaesthesia. Sometimes local analgesia is insufficient and potent opioid analgesia is necessary. The combination of potent opioid and midazolam can cause deep sedation and airway obstruction. These effects can be managed safely but involve extra resources. It would be safer if a technique could be developed that was both reliable and had a wide margin of safety. Prospective and retrospective audit data are available to help guide the choice of opioid and the doses. A randomised controlled trial is needed to test the efficacy and safety of these combinations.

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures under sedation with ketamine, how can the vomiting be reduced?

Why it is important

Ketamine is demonstrated to have a strong efficacy and safety profile in enabling safe sedation and as an analgesic drug useful for painful procedures in children and young people. Its main side effect is vomiting in approximately 10% of patients. No data is available on whether antiemetic drugs prevent vomiting. The GDG suggested an RCT study comparing ketamine + placebo versus ketamine with antiemetic

- For children and young people under the age of 19 undergoing diagnostic or therapeutic procedures, are procedures carried out under sedation more safe, effective and cost effective than those carried out under general anaesthesia?

Why it is important

Anaesthesia or an “Anaesthetist led service” has the advantage over sedation because it usually has faster onset and offset and is more predictable. It generally requires admission to hospital; it may be more expensive and is a scarce resource. Data comparing the efficiency of sedation in comparison with anaesthesia for certain procedures are not available. Models of care need to be developed and studied to whether anaesthesia or sedation gives the best value for money. With such data, efficient services can be planned.

- For children and young people under the age of 19 undergoing endoscopy, is propofol (with or without: analgesia, another drug or psychological techniques) effective, safe and cost effective for sedation (at minimal and moderate levels) in comparison with midazolam (with or without opioids) or with general anaesthesia?

Why it is important

Propofol is a short acting anaesthetic agent that can be used to achieve any target sedation level. The dose necessary for gastrointestinal endoscopy however usually has a tendency to cause anaesthesia albeit for a short period of time. It would be helpful to know the dose limitation that is unlikely to cause deep sedation because this dose may be effective and well tolerated enough. Moderate sedation with propofol could be compared with another sedation technique such as midazolam with or without opioid. It could also be compared with a general anaesthetic dose of propofol.

- For children and young people under the age of 19 undergoing painful procedures, is propofol effective and safe for sedation in comparison with ketamine?

Why it is important

Both ketamine and propofol are well tolerated and effective drugs suitable for painful procedures. Propofol however has a tendency to cause deep sedation and anaesthesia in which the airway and breathing may need an intervention or support. Ketamine has few appreciable effects on the airway and breathing but has a longer recovery time than propofol and causes vomiting.

- What are the safety and efficacy profiles of sedation techniques in current practice?

Why it is important

There are no data on the safety of sedation in the UK. A large prospective database of sedation cases, that includes data on drugs, procedures, the depth of sedation and complications, would help to define the safety of sedation and also actively promote safe practice. The GDG suggests that a national registry for paediatric sedation is established to help create a database with sufficient data.

- Is patient-controlled sedation with propofol feasible in adolescents and children?

Why it is important

Propofol in low dose is an excellent anxiolytic. Patient-controlled sedation has been validated in adults undergoing dental procedures and endoscopy for safety and efficacy. Giving the patient control of their sedation has important psychological benefits. The study would involve developing new pump technology, paediatric software and a child friendly patient-activation system. There would have to be an open pilot evaluation to establish safety and efficacy followed by a randomised-controlled trial versus IV midazolam.

7 Swimming in the sea of uncertainty in relation to sedation experience for children and young people undergoing diagnostic and therapeutic procedures

"To study the phenomenon of disease without books is to sail an uncharted sea, whilst to study books without patients is not to go to sea at all"

Osler (circa 1900)

7.1 Introduction

The importance of patient input to healthcare is not underestimated, but rarely is it properly achieved in providing real-time comment on how the experience has been shaped and the resultant impact of this experience on the patient's approach to future healthcare interventions. Whilst this has been achieved in adult populations to varying degrees of success, in the children's and young people population this is extremely rare, and little is reported in the literature. Having children and young people represented on the GDG is of course standard practice in NICE guideline development, but this has almost uniquely been through advocacy of carers. In trying to understand the challenges of providing a safe and effective sedation service, this feedback is crucial in determining how experts interpret evidence and remain sensitive to key clinical issues that impact on the child or young person receiving sedation. Early in development the NCGC in supporting this guideline and with the agreement from NICE made an ambitious decision to try and establish a snapshot of what it is like to be a child receiving sedation across a range of clinical contexts. The benefit of collecting real-time feedback in informing and shaping recommendations for practice is self evident, and through engagement with a developing methodology (National Paediatric Toolkit), the NCGC commissioned some primary data collection at Alder Hey Children's NHS Foundation Trust. The Trust is well positioned as England's first paediatric health promoting hospital accredited by the World Health Organisation and is one of Europe's biggest and busiest children's hospitals, providing care for over 200,000 children each year.

7.2 Development and conduct of the survey

The survey was carried out as part of a pilot project, with this particular survey focus being added to a menu of surveys administered within the Trust. The content of the survey was shaped by a subgroup of the GDG, with clinicians, technical team members and both patient carer representatives involved in the shaping of the questions asked. These were reviewed and signed off in consultation with the rest of the GDG and NICE, and were targeted at children undergoing painful and non-painful procedures requiring sedation. The questionnaire was administered using the National Paediatric Toolkit (NPT) software via hand-held, touch screen computers, a developing technology that is easy to use by even young children (over the age of four).

The NPT concept has been developed by Alder Hey Children's NHS Foundation Trust in partnership with Priority Research Ltd; throughout its development, children and young people were closely involved and contributed many ideas which have been incorporated into the current data collecting system.

The NPT was considered the system of choice for administering this survey because of a variety of unique advantages that it offers. These include:

- an engaging, cartoon format to maintain children's interest
- a large array of over 900 pre-defined questions, each worded differently for four developmental levels
- all questions available in eleven languages
- full voice-over for all text in all languages
- Disability Discrimination Act (1995) compliant for sensory, visual and hearing impairment
- real-time data collection and reporting.

The pilot ran from early November 2009 for 4 months and was conducted by experienced Alder Hey staff members previously engaged in similar types of data collection using the NPT.

7.3 Survey conduct approval

Patient opinion surveys are growing increasingly in both their conduct and importance, and this helps shape and reshape service delivery in different care settings. Contextually, until recently, this type of opinion seeking would have been viewed as primary research activity and therefore requiring ethics approval via a local committee or through a national committee, particularly relevant if this were multicentre research. Following changes in approach, seeking patient opinion is more latterly viewed as part of a quality improvement cycle, and is becoming more and more embedded into routine NHS Trust processes.

For this survey, approval and advice was sought and gained from Alder Hey NHS Foundation Trust's Head of Research and Ethics, Dr Matthew Peak.

7.4 Recruitment

A total of 70 patients undergoing a wide range of procedures were invited to take part, and 63 consented to do so. All departments and clinical areas within the hospital where patients receive sedation participated in the pilot.

7.5 Limitations of the survey

The limitations of the survey are important to note as this methodology will only describe the experience of the target population in one place at one time event. The 'snapshot' nature if surveys are extremely useful in determining the nature of patient experience and care interventions on a particular day. These cannot be generalised to other settings but findings are extremely helpful if repeat measurement is established so that a time series of events are recorded. Data are also useful, as in this case, when supporting other data (clinical and cost effectiveness reviews, consensus development), because when triangulated with this 'other' data inevitably enables the GDG in this case to build a clearer picture of what is happening and how to plan improvements in care and experience outcome.

7.6 Summary of main findings

7.6.1 Demographics

- The sample had an even spread of male and female children (44% male, 46% female, 10% not recorded) and covered a broad age range from under 4 to over 16 years of age.
- All except one were accompanied by a parent or carer, and for those children who could not complete the questionnaire themselves, a parent or carer were in a good position to do so (as expected, this was mostly younger children). Acceptability and usability of the system was such that nearly 1 in 4 (22%) of the under 4 age group were able to complete the survey themselves.
- Of the 23 children aged 9 and over, only one child aged eleven did not complete the survey themselves.
- Only four children (6%) were of black or minority ethnic origin.

7.6.2 Clinically relevant data

The most frequent clinical areas, accounting for almost two thirds of the sample, were:

- burns (21%)
- medical and renal day cases (17%)
- radiology (16%)

- accident and emergency (10%).

The most common agents used for sedation were:

- nitrous oxide (48%)
- midazolam (30%)
- oral morphine (14%)

Five procedures accounted for over half of the sample:

- change of wound dressings (22%)
- urodynamics (11%)
- intra-articular steroid injections (10%)
- cannulation (6%)
- removal of chest drains (6%).

7.6.3 Experience of children and young people receiving sedation

Ratings of satisfaction with information and consent issues were high:

- The people looking after me were nice to me and helped me feel OK (98%).
- I was told everything I wanted to know about what would happen (97%).
- I was told enough about the sedation (medicine that would make me feel OK and sleepy) (95%).
- I had time to ask any questions I wanted (91%).
- I was told enough about how I might feel (89%).
- I was taught things I could do to help me feel OK with what would happen (78%).

Patients were asked to rank their experience of pain, fear and upset on a six-point scale from 'Not at all' to 'As much as I can imagine'. The criterion for a positive result was a rating in the two lowest categories, that is 'Not at all' or 'Just a little bit'.

- Before the procedure, 56% were either not scared or just a little bit scared, and 11% said 'As much as I can imagine'.
- After receiving sedation, these figures were 80% and zero respectively.
- 70% reported no or little pain after sedation, and 86% no or little upset afterwards.

7.6.4 Other outcomes of interest

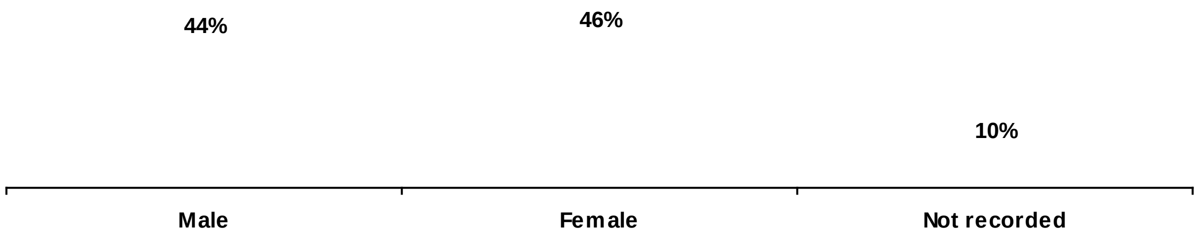
As would be expected, the degree of amnesia was dependent on the agent used; 13 of the 16 respondents who said they remembered "everything" had received Entonox, whilst of the 13 who received the benzodiazepine, five remembered "nothing" and five "just a little bit".

Post procedural nausea was related only to the degree of upset felt afterwards; those who felt more upset were more likely to report nausea (p = 0.019) but the direction of causality is not clear.

Only four patients said that they would not want to receive sedation again if undergoing the same procedure; this was significantly related to only two variables, both ratings of distress during the procedure after sedation. All four reported more than "just a little" pain during the procedure (p = 0.006) and being more than "just a little bit" scared (p = 0.001).

Demographics: Gender

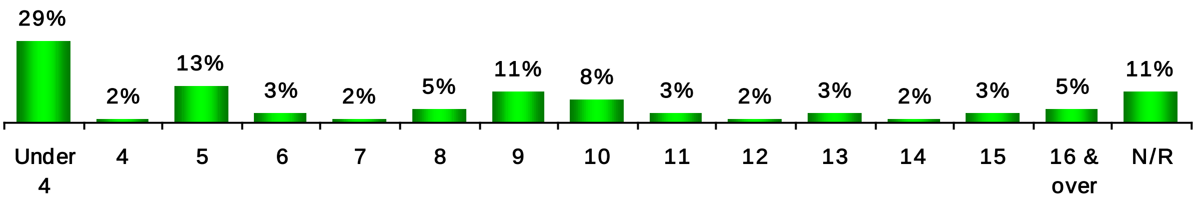
Base: N = 63



The sample had an even spread of male and female patients and covered a broad age range. All except one were accompanied by a parent or carer.

Demographics: Age range of participants

Base: N = 63



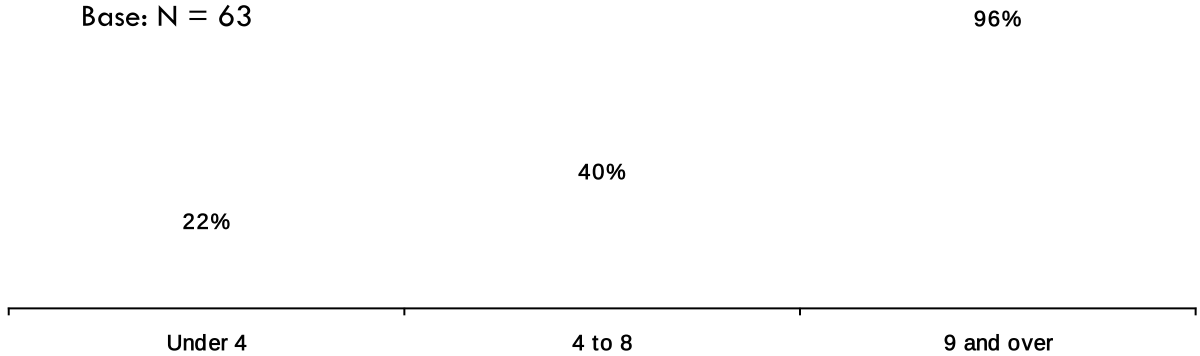
Demographics: Ethnic origin

Base: N = 63

	White			*Mixed*				*Asian or Asian British*					*Black or Black British*			*Other*			
	British	**Irish**	**Other White**	**White & Black Caribbean**	**White & Black African**	**White & Asian**	**Other mixed**	**Indian**	**Pakistani**	**Bangladeshi**	**Chinese**	**Other Asian**	**Caribbean**	**African**	**Other black**	**Other ethnic group**	**Gypsy or traveller**	**N/R**	**Base**
%	79	1.6	1.6	0	1.6	0	0	1.6	0	0	0	0	0	0	0	0	0	14	*100*
N	50	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	9	*63*

Demographics: Percentage of children completing the survey themselves

Base: N = 63



Parents or carers assisted children who could not complete the questionnaire themselves, and as would be expected this was mostly the younger children. Nevertheless, the acceptability of the system was such that 22% of the under fours were able to complete the survey themselves.

Of the 23 children aged 9 years and over, only one child aged eleven did not complete the survey themselves.

Demographics: Range of clinical areas relating to the child or young person's procedural sedation

Base: N = 63

Clinical area	N	%
Medical & renal day cases	11	17
Burns 1	11	17
Radiology	10	16
Accident & Emergency	6	9.5
Cardiac inpatients	4	6.3
Burns 2	4	6.3
Oncology	2	3.2
General surgery	2	3.2
Orthopaedics	1	1.6
High Dependence Unit	1	1.6
Neuro-medical	1	1.6
General medical	1	1.6
Cardiac outpatients	1	1.6
Not recorded	8	13

Within the survey, a large number of differing clinical contexts and therefore clinical teams are represented, which is very encouraging given the participants positive experience.

Demographics: Range of medication used relating to the child or young person's procedural sedation

Base: N = 63

Medication used	N	%
Entonox	30	48%
Midazolam	19	30%
Oral morphine	9	14%
Chloral hydrate	1	1.6%
IV morphine	1	1.6%
Oral ketamine	1	1.6%
IV ketamine	1	1.6%
Not recorded	11	18

Decisions made by the GDG when reviewing the initial scope and resulting clinical questions helped focus the pharmacological interventions review to what agents were in common use. The survey results reflect those discussions in that all of the above agents were systemically reviewed, with oral morphine being reviewed when used in combination. The single use of oral morphine is not advised. Propofol as a single agent it was not used at all in this large NHS Foundation Trust.

Demographics: Range of clinical procedure chosen in relation to the child or young person's procedural sedation

Base: N = 63

Procedure	N	%
Change of wound dressings	14	22
Urodynamics	7	11
Intra-articular steroid injections	6	10
Other	6	10
Cannulation	4	6.3
Removal of chest drains	4	6.3
Gamma camera	3	4.8
Botox injections	2	3.2
Removal of sutures	2	3.2
Removal of wound drains	2	3.2
MRI	1	1.6
Lumbar puncture	1	1.6
Removal of wires	1	1.6
Catheter insertion	1	1.6
Changing of line position	1	1.6
Not recorded	8	13

The survey results are also helpful regarding the types of procedure anticipated in relation to the target guideline population. The one clear obvious omission is dental treatment, which the survey was not able to include.

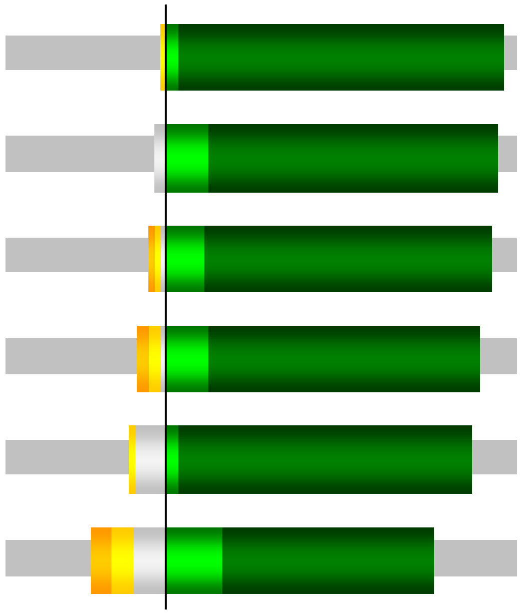
The survey results within the context of the clinically important issues are extremely useful as they, for the most part, affirm the clinical interpretation of the evidence by the GDG in relation to targeting key clinical contexts, key clinical procedures and key clinical interventions. That said, the way children and young people are supported through the sedation experience is of perhaps the greatest interest.

The experience of children and young people undergoing procedural sedation:

Part 1: Information and support

Base: N = 63

Statement	Rating	% agree
The people looking after me were nice to me and helped me feel OK		98
I was told everything I wanted to know about what would happen		97
I was told enough about the sedation (medicine that would make me feel OK and sleepy)		95
I had time to ask any questions I wanted		91
I was told enough about how I might feel		89
I was taught things I could do to help me feel OK with what would happen		78



Key: **Disagree a lot** | **Disagree a bit** | **In the middle** | **Agree a bit** | **Agree a lot**

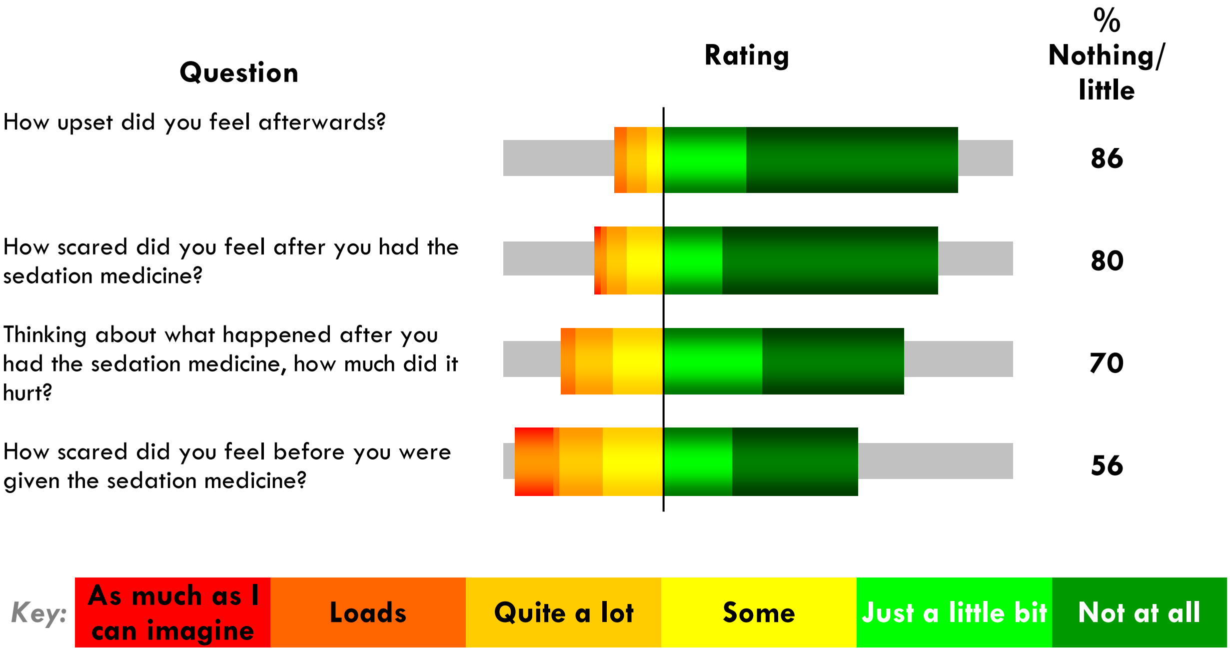
The GDG subgroup had carefully considered the type of questions we wanted to ask; these covered the pre-procedural phase when the child or young person is being prepared (information, consent, visualisation), during procedure (amnesic effect, pain free) and the post procedural phase (amnesic effect, nausea, emotional response, preparedness for repeat intervention under sedation).

The questions were then in discussion with Priority Research who have experience in conducting this type of survey finalised to ensure they would be understood by all age ranges and that they would readily translate into the range of languages used.

The experience of children and young people undergoing procedural sedation:

Part 2: Emotional engagement and memory recall

Base: N = 63



The survey results are particularly interesting in this area as they indicate that children and young people have an extremely positive experience of sedation in relation to a wide range and variety of clinical procedures and clinical settings. The responses indicate little variation in practice in this one NHS Foundation Trust, and are indicative of the benefit that clinical guidance can bring when clinical and patient pathways are followed to plan and prepare the patient and ensure their experience is positive.

The results are seen as indicating that much of this is bearing this positive outcome.

The experience of children and young people undergoing procedural sedation:

Part 1 and 2 survey detail in relation to responses and percentage breakdown

Base: N = 63

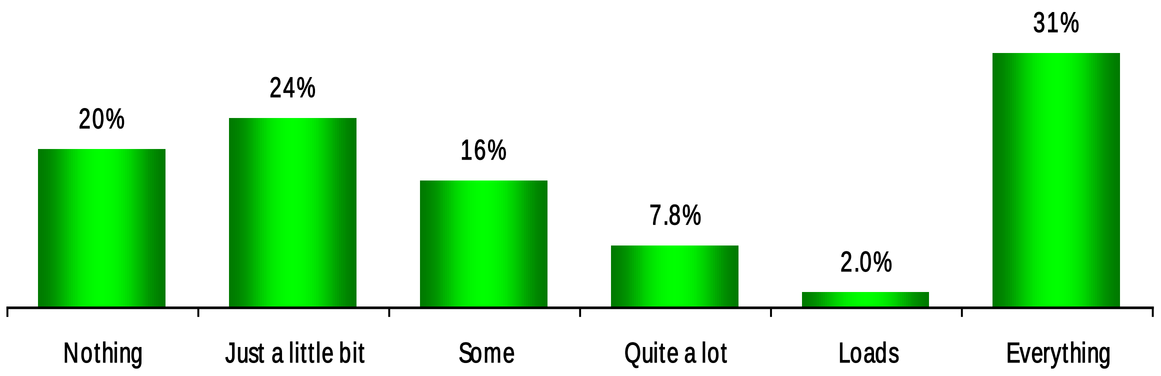
	Percentages					*Further details*			
	Disagree a lot	Disagree a bit	In the middle	Agree a bit	Agree a lot	Base	N/R%	Response	Total base
I was told everything I wanted to know about what would happen	0	0	3.5	12	84	*57*	*6.6*	*93*	*63*
I was told enough about the sedation	1.8	1.8	1.8	11	84	*55*	*9.8*	*90*	*63*
I was told enough about how I might feel	0	1.8	9.1	3.6	85	*55*	*9.8*	*90*	*63*
I was taught things I could do to help me feel OK with what would happen	6	6	10	16	62	*50*	*18*	*82*	*63*
I had time to ask any questions I wanted	3.6	3.6	1.8	13	79	*56*	*8.2*	*92*	*63*
The people looking after me were nice to me and helped me feel OK	0	1.8	0	3.6	95	*56*	*8.2*	*92*	*63*

	Percentages						*Further details*			
	As much as I can imagine	Loads	Quite a lot	Some	Just a little bit	Not at all	Base	N/R%	Response	Total base
How upset did you feel afterwards?	0	3.6	5.5	5.5	24	62	*55*	*13*	*87*	*63*
How scared did you feel after you had the sedation medicine?	1.9	1.9	5.6	11	17	63	*54*	*14*	*86*	*63*
Thinking about what happened after you had the sedation medicine, how much did it hurt?	0	3.8	11	15	28	42	*53*	*16*	*84*	*63*
How scared did you feel before you were given the sedation medicine?	11	1.8	13	18	20	36	*55*	*13*	*87*	*63*

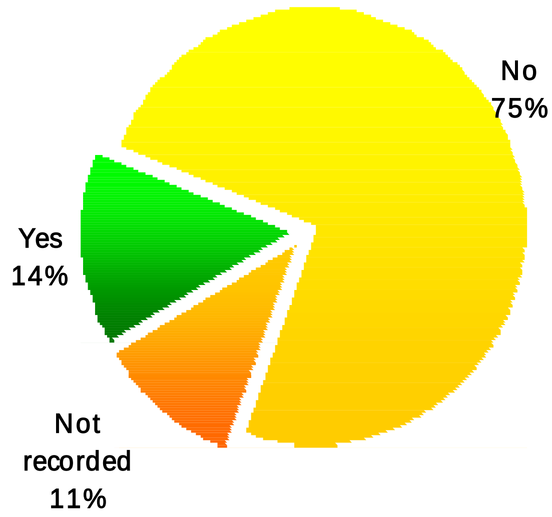
The experience of children and young people undergoing procedural sedation:

Part 3 Outcomes

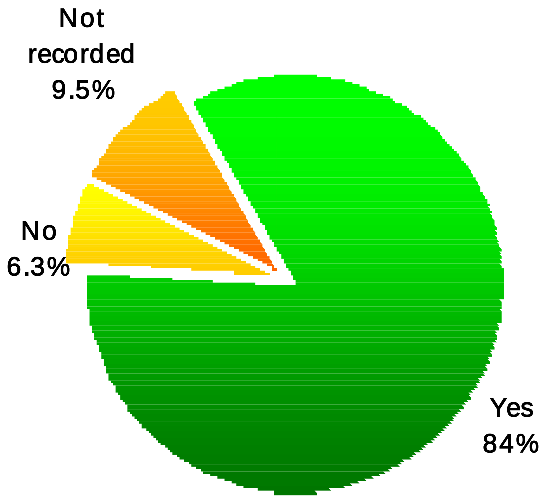
Amnesic effect of sedation in relation to memory of procedure



Did you feel sick after the procedure?



Would you want sedation again if you had to have more treatment?



The above outcomes were related to other variables. As would be expected, the degree of amnesia was dependent on the agent used; 13 of the 16 respondents who said they remembered "everything" had received Entonox, whilst of the 13 who received the benzodiazepine, five remembered "nothing" and five "just a little bit".

Post procedural nausea was related only to the degree of upset felt afterwards; those who felt more upset were more likely to report nausea ($p = 0.019$) but the direction of causality is not clear.

Only four patients said that they would not want to receive sedation again if undergoing the same procedure; this was significantly related to only two variables, both ratings of distress during the procedure after sedation. All four reported more than "just a little" pain during the procedure ($p = 0.006$) and being more than "just a little bit" scared ($p = 0.001$).

The Questionnaire Content (respondent) and Data Summary can be found in appendixes J and K, respectively.

7.7 Conclusions

The survey results within the context of the clinically important issues are extremely useful as they by large, affirm the clinical interpretation of the evidence by the GDG in relation to targeting key clinical contexts, key clinical procedures, key clinical interventions. That said, the way children and young people are supported through the sedation experience is of perhaps the greatest interest.

The survey provided the GDG with an immediate contextual opportunity to test areas of importance in relation to all aspects of the scope, and in particular areas relating to the preparation and experience of the child or young person receiving sedation. Survey findings supported the shaping of clinical questions relating to pharmacological interventions reviews and what agents were in commonly used, allowing for these to be systematically reviewed in single or combination therapies. The absence of propofol as a single agent is noted that it was not used at all in this large NHS Foundation Trust. Propofol is reported in the evidence to recommendations as having a wide margin of safety, requiring additional training as deep sedation may result despite a different target level of sedation being aimed for.

The guideline provides the basis to see this aspect of sedation practice change. The survey provided contextual evidence that supports the outcomes of the narrative review relating to psychological support. During the pre procedural phase when the child or young person is being prepared, clear information, informed consent and the use of visualisation in preparation were highlighted as areas that are important in determining a positive experience with successful outcome. The results of the survey relating to the amnesic effect and pain management affect are less strong, but support consistently the findings of evidence reviews (particular pain management) and undoubtedly helped the GDG shape recommendations with greater confidence.

The higher level questions of satisfaction relating to the child or young person's experience are very strong indicating when undergoing sedation, an extremely positive experience is reported in relation to a wide range and variety of clinical procedures and clinical settings (dental care is not part of the survey population). Responses indicate little variation in practice in one NHS Foundation Trust, and are indicative of the benefit that the clinical guideline will have in shaping clinical and patient pathways as part of the implementation strategy.

8 Bibliography

1 Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. A Report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology*. 1996; 84(2):459-471. *(Guideline Ref ID 16022)*

2 *Consent - What You Have a Right to Expect: A Guide for Children and Young People*. London: Department of Health; 2001. *(Guideline Ref ID 15987)*

3 *Consent - What You Have a Right to Expect: A Guide for Parents*. London: Department of Health; 2001. *(Guideline Ref ID 15989)*

4 *Consent - What You Have a Right to Expect: A Guide for Relatives and Carers*. London: Department of Health; 2001. *(Guideline Ref ID 15990)*

5 *Consent: A Guide for People With Learning Disabilities*. London: Department of Health; 2001. *(Guideline Ref ID 15988)*

6 Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology*. 2002; 96(4):1004-1017. *(Guideline Ref ID 16021)*

7 *Restraining, Holding Still and Containing Children and Young People. Guidance for Nursing Staff*. London: Royal College of Nursing; 2003. *(Guideline Ref ID 15991)*

8 *Perioperative Fasting in Adults and Children. An RCN Guideline for the Multidisciplinary Team*. London: Royal College Of Nursing; 2005. *(Guideline Ref ID 15993)*

9 *Standards for Conscious Sedation in Dentistry: Alternative Techniques. A Report From the Standing Committee on Sedation for Dentistry*. London: Royal College of Surgeons of England; 2007. *(Guideline Ref ID 15950)*

10 Acworth JP, Purdie D, Clark RC. Intravenous Ketamine Plus Midazolam Is Superior to Intranasal Midazolam for Emergency Paediatric Procedural Sedation. *Emergency Medicine Journal*. 2001; 18(1):39-45. *(Guideline Ref ID 815)*

11 Addelston H. Your Child's First Visit to the Dentist. *Child Study*. 1954; 31:33. *(Guideline Ref ID 15980)*

12 Agrawal D, Manzi SF, Gupta R, Krauss B. Preprocedural Fasting State and Adverse Events in Children Undergoing Procedural Sedation and Analgesia in a Pediatric Emergency Department. *Annals of Emergency Medicine*. 2003; 42(5):636-646. *(Guideline Ref ID 599)*

13 Al-Zahrani AM, Wyne AH, Sheta SA. Comparison of Oral Midazolam With a Combination of Oral Midazolam and Nitrous Oxide-Oxygen Inhalation in the Effectiveness of Dental Sedation for Young Children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*. 2009; 27(1):9-16. *(Guideline Ref ID 15922)*

14 Amanor-Boadu SD. The Effect of Parental Presence at Induction of Anaesthesia on the Behaviour of Unsedated Nigerian Children Presenting for Day-Case Anaesthesia. *West African Journal of Medicine*. 2002; 21(1):28-30. *(Guideline Ref ID 15954)*

15 American Academy of Pediatric Dentistry Clinical Affairs Committee and American Academy of Pediatric Dentistry Council on Clinical Affairs. *Guideline on Behavior Guidance for the Pediatric Dental Patient*. 2008. *(Guideline Ref ID 65)*

16 Antmen B, Sasmaz I, Birbicer H, Ozbek H, Burgut R, Isik G, Kilinc Y. Safe and Effective Sedation and Analgesia for Bone Marrow Aspiration Procedures in Children With Alfentanil, Remifentanil and Combinations With Midazolam. *Paediatric Anaesthesia*. 2005; 15(3):214-219. *(Guideline Ref ID 426)*

17 Arai Y-C, Ito H, Kandatsu N, Kurokawa S, Kinugasa S, Komatsu T. Parental Presence During Induction Enhances the Effect of Oral Midazolam on Emergence Behavior of Children Undergoing General Anesthesia. *Acta Anaesthesiologica Scandinavica*. 2007; 51(7):858-861. *(Guideline Ref ID 718)*

18 Arai Y-C, Kandatsu N, Ito H, Sato Y, Satake Y, Mizutani M, Ushida T, Komatsu T. Induction and Emergence Behavior of Children Undergoing General Anesthesia Correlates With Maternal Salivary Amylase Activity Before the Anesthesia. *Acta Anaesthesiologica Scandinavica*. 2008; 52(2):285-288. *(Guideline Ref ID 680)*

19 Atkinson P, Chesters A, Heinz P. Pain Management and Sedation for Children in the Emergency Department. *BMJ*. 2009; 339:b4234. *(Guideline Ref ID 15925)*

20 Averley PA, Girdler NM, Bond S, Steen N, Steele J. A Randomised Controlled Trial of Paediatric Conscious Sedation for Dental Treatment Using Intravenous Midazolam Combined With Inhaled Nitrous Oxide or Nitrous Oxide/Sevoflurane. *Anaesthesia*. 2004; 59(9):844-852. *(Guideline Ref ID 486)*

21 Babl FE, Oakley E, Puspitadewi A, Sharwood LN. Limited Analgesic Efficacy of Nitrous Oxide for Painful Procedures in Children. *Emergency Medicine Journal*. 2008; 25(11):717-721. *(Guideline Ref ID 4434)*

22 Babl FE, Oakley E, Seaman C, Barnett P, Sharwood LN. High-Concentration Nitrous Oxide for Procedural Sedation in Children: Adverse Events and Depth of Sedation. *Pediatrics*. 2008; 121(3):e528-e532. *(Guideline Ref ID 60)*

23 Babl FE, Puspitadewi A, Barnett P, Oakley E, Spicer M. Preprocedural Fasting State and Adverse Events in Children Receiving Nitrous Oxide for Procedural Sedation and Analgesia. *Pediatric Emergency Care*. 2005; 21(11):736-743. *(Guideline Ref ID 15927)*

24 Barbi E, Gerarduzzi T, Marchetti F, Neri E, Verucci E, Bruno I, Martelossi S, Zanazzo G, Sarti A, Ventura A. Deep Sedation With Propofol by Nonanesthesiologists: a Prospective Pediatric Experience. *Archives of Pediatrics and Adolescent Medicine*. 2003; 157(11):1097-1103. *(Guideline Ref ID 8298)*

25 Barbi E, Petaros P, Badina L, Pahor T, Giuseppin I, Biasotto E, Martelossi S, Di LG, Sarti A, Ventura A. Deep Sedation With Propofol for Upper Gastrointestinal Endoscopy in Children, Administered by Specially Trained Pediatricians: A Prospective Case Series With Emphasis on Side Effects. *Endoscopy*. 2006; 38(4):368-375. *(Guideline Ref ID 197)*

26 Bassett KE, Anderson JL, Pribble CG, Guenther E. Propofol for Procedural Sedation in Children in the Emergency Department. *Annals of Emergency Medicine*. 2003; 42(6):773-782. *(Guideline Ref ID 591)*

27 Bevan JC, Johnston C, Haig MJ, Tousignant G, Lucy S, Kirnon V, Assimes IK, Carranza R. Preoperative Parental Anxiety Predicts Behavioural and Emotional Responses to Induction of Anaesthesia in Children. *Canadian Journal of Anaesthesia*. 1990; 37(2):177-182. *(Guideline Ref ID 511)*

28 Blesch P, Fisher ML. The Impact of Parental Presence on Parental Anxiety and Satisfaction. *AORN Journal*. 1996; 63(4):761-768. *(Guideline Ref ID 15952)*

29 Blount RL, Bachanas PJ, Powers SW, Cotter MC, Franklin A, Chaplin W, Mayfield J, Henderson M, Blount SD. Training Children to Cope and Parents to Coach Them During Routine Immunizations: Effects on Child, Parent, and Staff Behaviors. *Behavior Therapy*. 1992; 23(4):689-705. *(Guideline Ref ID 16007)*

30 Blount RL, Bunke V, Cohen LL, Forbes CJ. The Child-Adult Medical Procedure Interaction Scale-Short Form (CAMPIS-SF): Validation of a Rating Scale for Children's and Adults' Behaviors During Painful Medical Procedures. *Journal of Pain and Symptom Management*. 2001; 22(1):591-599. *(Guideline Ref ID 16016)*

31 Blount RL, Corbin SM, Sturges JW, Wolfe VV, Prater JM, James LD. The Relationship Between Adults' Behavior and Child Coping and Distress During BMA/LP Procedures: A Sequential Analysis. *Behavior Therapy*. 1989; 20(4):585-601. *(Guideline Ref ID 16013)*

32 Bosenberg AT, Williams GD, Reddy D. Attitudes Towards Parental Presence at Induction of Anaesthesia. *South African Medical Journal*. 1996; 86(6):664-667. *(Guideline Ref ID 389)*

33 Bowling A. *Research Methods in Health*. 2nd ed. Maidenhead: Open University Press; 2002. *(Guideline Ref ID 15810)*

34 Calipel S, Lucas-Polomeni M-M, Wodey E, Ecoffey C. Premedication in Children: Hypnosis Versus Midazolam. *Paediatric Anaesthesia*. 2005; 15(4):275-281. *(Guideline Ref ID 857)*

35 Cameron JA, Bond MJ, Pointer SC. Reducing the Anxiety of Children Undergoing Surgery: Parental Presence During Anaesthetic Induction. *Journal of Paediatrics and Child Health*. 1996; 32(1):51-56. *(Guideline Ref ID 15865)*

36 Campbell C, Hosey MT, McHugh S. Facilitating Coping Behavior in Children Prior to Dental General Anesthesia: a Randomized Controlled Trial. *Paediatric Anaesthesia*. 2005; 15(10):831-838. *(Guideline Ref ID 15866)*

37 Cassidy KL, Reid GJ, McGrath PJ, Finley GA, Smith DJ, Morley C, Szudek EA, Morton B. Watch Needle, Watch TV: Audiovisual Distraction in Preschool Immunization. *Pain Medicine*. 2002; 3(2):108-118. *(Guideline Ref ID 16002)*

38 Cechvala MM, Christenson D, Eickhoff JC, Hollman GA. Sedative Preference of Families for Lumbar Punctures in Children With Acute Leukemia: Propofol Alone or Propofol and Fentanyl. *Journal of Pediatric Hematology/Oncology*. 2008; 30(2):142-147. *(Guideline Ref ID 48)*

39 Chundamala J, Wright JG, Kemp SM. An Evidence-Based Review of Parental Presence During Anesthesia Induction and Parent/Child Anxiety. *Canadian Journal of Anaesthesia*. 2009; 56(1):57-70. *(Guideline Ref ID 15982)*

40 Cohen LL, Bernard RS, Greco LA, McClellan CB. A Child-Focused Intervention for Coping With Procedural Pain: Are Parent and Nurse Coaches Necessary? *Journal of Pediatric Psychology*. 2002; 27(8):749-757. *(Guideline Ref ID 16003)*

41 Cohen LL, Blount RL, Panopoulos G. Nurse Coaching and Cartoon Distraction: an Effective and Practical Intervention to Reduce Child, Parent, and Nurse Distress During Immunizations. *Journal of Pediatric Psychology*. 1997; 22(3):355-370. *(Guideline Ref ID 16004)*

42 Connors K, Terndrup TE. Nasal Versus Oral Midazolam for Sedation of Anxious Children Undergoing Laceration Repair. *Annals of Emergency Medicine*. 1994; 24(6):1074-1079. *(Guideline Ref ID 1286)*

43 Cortellazzi P, Lamperti M, Minati L, Falcone C, Pantaleoni C, Caldiroli D. Sedation of Neurologically Impaired Children Undergoing MRI: a Sequential Approach. *Paediatric Anaesthesia*. 2007; 17(7):630-636. *(Guideline Ref ID 8308)*

44 Cote CJ, Wilson S. Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures: an Update. *Pediatrics*. 2006; 118(6):2587-2602. *(Guideline Ref ID 6)*

45 Coulthard P. Conscious Sedation Guidance. *Evidence-Based Dentistry*. 2006; 7(4):90-91. *(Guideline Ref ID 72)*

46 Cravero JP, Beach ML, Blike GT, Gallagher SM, Hertzog JH, Pediatric Sedation Research Consortium. The Incidence and Nature of Adverse Events During Pediatric Sedation/Anesthesia With Propofol for Procedures Outside the Operating Room: a Report From the Pediatric Sedation Research Consortium. *Anesthesia and Analgesia*. 2009; 108(3):795-804. *(Guideline Ref ID 8300)*

47 Dahlquist LM, Pendley JS, Power TG, Landthrip DS, Jones CL, Steuber CP. Adult Command Structure and Children's Distress During the Anticipatory Phase of Invasive Cancer Procedures. *Children's Health Care*. 2001; 30(2):151-167. *(Guideline Ref ID 16015)*

48 Dahlquist LM, Power TG, Carlson L. Physician and Parent Behavior During Invasive Pediatric Cancer Procedures: Relationships to Child Behavioral Distress. *Journal of Pediatric Psychology*. 1995; 20(4):477-490. *(Guideline Ref ID 16014)*

49 Dallman JA, Ignelzi MA, Jr., Briskie DM. Comparing the Safety, Efficacy and Recovery of Intranasal Midazolam Vs. Oral Chloral Hydrate and Promethazine. *Pediatric Dentistry*. 2001; 23(5):424-430. *(Guideline Ref ID 772)*

50 Davidson AJ, Shrivastava PP, Jamsen K, Huang GH, Czarnecki C, Gibson MA, Stewart SA, Stargatt R. Risk Factors for Anxiety at Induction of Anesthesia in Children: A

Prospective Cohort Study. *Paediatric Anaesthesia*. 2006; 16(9):919-927. *(Guideline Ref ID 782)*

51 De Sanctis Briggs V. Magnetic Resonance Imaging Under Sedation in Newborns and Infants: a Study of 640 Cases Using Sevoflurane. *Paediatric Anaesthesia*. 2005; 15(1):9-15. *(Guideline Ref ID 8289)*

52 Delbecq AL, Van de Ven AH, Gustafson DH. *Group Techniques For Program Planning: A Guide to Nominal Group and Delphi Processes*. Middleton, Wis: Green Briar Press; 1986. *(Guideline Ref ID 15811)*

53 Department of Health. *A Conscious Decision. A Review of the Use of General Anaesthesia and Conscious Sedation in Primary Dental* Care. London: Department of Health; 2000. *(Guideline Ref ID 15947)*

54 Dilli D, Dallar Y, Sorguc NH. Comparison of Ketamine Plus Midazolam Versus Ketamine for Sedation in Children During Lumbar Puncture. *Clinical Journal of Pain*. 2009; 25(4):349-350. *(Guideline Ref ID 2659)*

55 Dilli D, Dallar Y, Sorgui NH. Intravenous Ketamine Plus Midazolam Vs. Intravenous Ketamine for Sedation in Lumbar Puncture: a Randomized Controlled Trial. *Indian Pediatrics*. 2008; 45(11):899-904. *(Guideline Ref ID 4314)*

56 Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, Bonanno G, Russo A. Propofol Sedation With Fentanyl or Midazolam During Oesophagogastroduodenoscopy in Children. *European Journal of Anaesthesiology*. 2005; 22(11):848-852. *(Guideline Ref ID 334)*

57 Duff AJ. Incorporating Psychological Approaches into Routine Paediatric Venepuncture. *Archives of Disease in Childhood*. 2003; 88(10):931-937. *(Guideline Ref ID 15966)*

58 Ekbom K, Jakobsson J, Marcus C. Nitrous Oxide Inhalation Is a Safe and Effective Way to Facilitate Procedures in Paediatric Outpatient Departments. *Archives of Disease in Childhood*. 2005; 90(10):1073-1076. *(Guideline Ref ID 15942)*

59 Erden IA, Pamuk AG, Akinci SB, Koseoglu A, Aypar U. Comparison of Propofol-Fentanyl With Propofol-Fentanyl-Ketamine Combination in Pediatric Patients Undergoing Interventional Radiology Procedures. *Paediatric Anaesthesia*. 2009; 19(5):500-506. *(Guideline Ref ID 4356)*

60 Everitt IJ, Barnett P. Comparison of Two Benzodiazepines Used for Sedation of Children Undergoing Suturing of a Laceration in an Emergency Department. *Pediatric Emergency Care*. 2002; 18(2):72-74. *(Guideline Ref ID 737)*

61 Faddy SC, Garlick SR. A Systematic Review of the Safety of Analgesia With 50% Nitrous Oxide: Can Lay Responders Use Analgesic Gases in the Prehospital Setting? *Emergency Medicine Journal*. 2005; 22(12):901-908. *(Guideline Ref ID 8)*

62 Fanurik D, Koh JL, Schmitz ML. Distraction Techniques Combined With EMLA: Effects on IV Insertion Pain and Distress in Children. *Children's Health Care*. 2000; 29(2):87-101. *(Guideline Ref ID 1019)*

63 Fatovich DM, Jacobs IG. A Randomized, Controlled Trial of Oral Midazolam and Buffered Lidocaine for Suturing Lacerations in Children (the SLIC Trial). *Annals of Emergency Medicine*. 1995; 25(2):209-214. *(Guideline Ref ID 2763)*

64 Fauroux B, Onody P, Gall O, Tourniaire B, Koscielny S, Clement A. The Efficacy of Premixed Nitrous Oxide and Oxygen for Fiberoptic Bronchoscopy in Pediatric Patients: a Randomized, Double-Blind, Controlled Study. *Chest*. 2004; 125(1):315-321. *(Guideline Ref ID 546)*

65 Faust J, Melamed BG. Influence of Arousal, Previous Experience, and Age on Surgery Preparation of Same Day of Surgery and in-Hospital Pediatric Patients. *Journal of Consulting and Clinical Psychology*. 1984; 52(3):359-365. *(Guideline Ref ID 15979)*

66 Festa SA, Ferguson FS, Hauk M. Behavior Management Techniques in Pediatric Dentistry. *New York State Dental Journal*. 1993; 59(2):35-38. *(Guideline Ref ID 471)*

67 Fishbein M, Lugo RA, Woodland J, Lininger B, Linscheid T. Evaluation of Intranasal Midazolam in Children Undergoing Esophagogastroduodenoscopy. *Journal of Pediatric Gastroenterology and Nutrition*. 1997; 25(3):261-266. *(Guideline Ref ID 1089)*

68 Fortier MA, Chorney JM, Rony RY, Perret-Karimi D, Rinehart JB, Camilon FS, Kain ZN. Children's Desire for Perioperative Information. *Anesthesia and Analgesia*. 2009; 109(4):1085-1090. *(Guideline Ref ID 15961)*

69 Fox BE, O'Brien CO, Kangas KJ, Murphree AL, Wright KW. Use of High Dose Chloral Hydrate for Ophthalmic Exams in Children: a Retrospective Review of 302 Cases. *Journal of Pediatric Ophthalmology and Strabismus*. 1990; 27(5):242-244. *(Guideline Ref ID 63)*

70 Franck LS, Spencer C. Informing Parents About Anaesthesia for Children's Surgery: a Critical Literature Review. *Patient Education and Counseling*. 2005; 59(2):117-125. *(Guideline Ref ID 133)*

71 Fuks AB, Kaufman E, Ram D, Hovav S, Shapira J. Assessment of Two Doses of Intranasal Midazolam for Sedation of Young Pediatric Dental Patients. *Pediatric Dentistry*. 1994; 16(4):301-305. *(Guideline Ref ID 1297)*

72 Fukuta O, Braham RL, Yanase H, Kurosu K. The Sedative Effects of Intranasal Midazolam Administration in the Dental Treatment of Patients With Mental Disabilities. Part 2: Optimal Concentration of Intranasal Midazolam. *Journal of Clinical Pediatric Dentistry*. 1994; 18(4):259-265. *(Guideline Ref ID 1282)*

73 Gall O, Annequin D, Benoit G, Van Glabeke E, Vrancea F, Murat I. Adverse Events of Premixed Nitrous Oxide and Oxygen for Procedural Sedation in Children. *Lancet*. 2001; 358(9292):1514-1515. *(Guideline Ref ID 4005)*

74 Gauderer MWL, Lorig JL, Wastwood DW. Is There a Place for Parents in the Operating Room? *Journal of Pediatric Surgery*. 1989; 24(7):705-707. *(Guideline Ref ID 1162)*

75 General Dental Council. *Standards for Dental Professionals*. London: General Dental Council; 2005. *(Guideline Ref ID 15946)*

76 Gilger MA, Spearman RS, Dietrich CL, Spearman G, Wilsey J, Zayat MN. Safety and Effectiveness of Ketamine As a Sedative Agent for Pediatric GI Endoscopy. *Gastrointestinal Endoscopy*. 2004; 59(6):659-663. *(Guideline Ref ID 282)*

77 Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of Propofol/Fentanyl Versus Ketamine/Midazolam for Brief Orthopedic Procedural Sedation in a Pediatric Emergency Department. *Pediatrics*. 2003; 112(1 Pt 1):116-123. *(Guideline Ref ID 630)*

78 Golan G, Tighe P, Dobija N, Perel A, Keidan I. Clowns for the Prevention of Preoperative Anxiety in Children: a Randomized Controlled Trial. *Paediatric Anaesthesia*. 2009; 19(3):262-266. *(Guideline Ref ID 13)*

79 Green MC, McNiece WL. Preoperative Evaluation and Preparation of the Pediatric Patient. *Seminars in Pediatric Surgery*. 1992; 1(1):4-10. *(Guideline Ref ID 473)*

80 Green SM, Klooster M, Harris T, Lynch EL, Rothrock SG. Ketamine Sedation for Pediatric Gastroenterology Procedures. *Journal of Pediatric Gastroenterology and Nutrition*. 2001; 32(1):26-33. *(Guideline Ref ID 75)*

81 Green SM, Rothrock SG, Harris T, Hopkins GA, Garrett W, Sherwin T. Intravenous Ketamine for Pediatric Sedation in the Emergency Department: Safety Profile With 156 Cases. *Academic Emergency Medicine*. 1998; 5(10):971-976. *(Guideline Ref ID 86)*

82 Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hastdalen R, Hopkins GA, Garrett W, Westcott K. Intramuscular Ketamine for Pediatric Sedation in the Emergency Department: Safety Profile in 1,022 Cases. *Annals of Emergency Medicine*. 1998; 31(6):688-697. *(Guideline Ref ID 4172)*

83 Greenberg SB, Faerber EN, Aspinall CL. High Dose Chloral Hydrate Sedation for Children Undergoing CT. *Journal of Computer Assisted Tomography*. 1991; 15(3):467-469. *(Guideline Ref ID 61)*

84 Greenberg SB, Faerber EN, Aspinall CL, Adams RC. High-Dose Chloral Hydrate Sedation for Children Undergoing MR Imaging: Safety and Efficacy in Relation to Age. *American Journal of Roentgenology*. 1993; 161(3):639-641. *(Guideline Ref ID 8310)*

85 Hackworth SR, McMahon RJ. Factors Mediating Children's Health Care Attitudes. *Journal of Pediatric Psychology*. 1991; 16(1):69-85. *(Guideline Ref ID 15996)*

86 Haeberli S, Grotzer MA, Niggli FK, Landolt MA, Linsenmeier C, Ammann RA, Bodmer N. A Psychoeducational Intervention Reduces the Need for Anesthesia During Radiotherapy for Young Childhood Cancer Patients. *Radiation Oncology*. 2008; 3:17. *(Guideline Ref ID 15879)*

87 Hannallah RS, Larach MG. Should Parents Be Permitted to Be Present for Induction of Anesthesia in Children? *Anesthesiology Review*. 1993; 20(4):141-146. *(Guideline Ref ID 1125)*

88 Harrison A. Preparing Children for Venous Blood Sampling. *Pain*. 1991; 45(3):299-306. *(Guideline Ref ID 15972)*

89 Harrison M, Nutting L. Repeat General Anaesthesia for Paediatric Dentistry. *British Dental Journal*. 2000; 189(1):37-39. *(Guideline Ref ID 15944)*

90 Hartgraves PM, Primosch RE. An Evaluation of Oral and Nasal Midazolam for Pediatric Dental Sedation. *Journal of Dentistry for Children*. 1994; 61(3):175-181. *(Guideline Ref ID 1303)*

91 Havel CJ, Jr., Strait RT, Hennes H. A Clinical Trial of Propofol Vs Midazolam for Procedural Sedation in a Pediatric Emergency Department. *Academic Emergency Medicine*. 1999; 6(10):989-997. *(Guideline Ref ID 903)*

92 Heistein LC, Ramaciotti C, Scott WA, Coursey M, Sheeran PW, Lemler MS. Chloral Hydrate Sedation for Pediatric Echocardiography: Physiologic Responses, Adverse Events, and Risk Factors. *Pediatrics*. 2006; 117(3):e434-e441. *(Guideline Ref ID 10)*

93 Hickmott KC, Shaw EA, Goodyer I, Baker RD. Anaesthetic Induction in Children: the Effects of Maternal Presence on Mood and Subsequent Behaviour. *European Journal of Anaesthesiology*. 1989; 6(2):145-155. *(Guideline Ref ID 15953)*

94 Hollman GA, Schultz MM, Eickhoff JC, Christenson DK. Propofol-Fentanyl Versus Propofol Alone for Lumbar Puncture Sedation in Children With Acute Hematologic Malignancies: Propofol Dosing and Adverse Events. *Pediatric Critical Care Medicine*. 2008; 9(6):616-622. *(Guideline Ref ID 8315)*

95 Houpt M. Management of Child Behavior in the Dental Environment. *Compendium*. 1972; 14(1):64-70. *(Guideline Ref ID 469)*

96 Houpt M, Manetas C, Joshi A, Desjardins P. Effects of Chloral Hydrate on Nitrous Oxide Sedation of Children. *Pediatric Dentistry*. 1989; 11(1):26-29. *(Guideline Ref ID 1564)*

97 Houpt MI, Sheskin RB, Koenigsberg SR, DesJardins PJ, Shey Z. Assessing Chloral Hydrate Dosage for Young Children. *ASDC Journal of Dentistry for Children*. 1985; 52(5):364-369. *(Guideline Ref ID 3625)*

98 Hulland SA, Freilich MM, S+ándor GKB. Nitrous Oxide-Oxygen or Oral Midazolam for Pediatric Outpatient Sedation. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontology*. 2002; 93(6):643-646. *(Guideline Ref ID 517)*

99 Iannalfi A, Bernini G, Caprilli S, Lippi A, Tucci F, Messeri A. Painful Procedures in Children With Cancer: Comparison of Moderate Sedation and General Anesthesia for Lumbar Puncture and Bone Marrow Aspiration. *Pediatric Blood and Cancer*. 2005; 45(7):933-938. *(Guideline Ref ID 2174)*

100 Ingebo KR, Rayhorn NJ, Hecht RM, Shelton MT, Silber GH, Shub MD. Sedation in Children: Adequacy of Two-Hour Fasting. *Journal of Pediatrics*. 1997; 131(1 Pt 1):155-158. *(Guideline Ref ID 124)*

101 Jameson K, Averley PA, Shackley P, Steele J. A Comparison of the 'Cost Per Child Treated' at a Primary Care-Based Sedation Referral Service, Compared to a General Anaesthetic in Hospital. *British Dental Journal*. 2007; 203(6):E13. *(Guideline Ref ID 4213)*

102 Johnston CC, Bevan JC, Haig MJ, Kirnon V, Tousignant G. Parental Presence During Anesthesia Induction. A Research Study. *AORN Journal*. 1988; 47(1):187-194. *(Guideline Ref ID 15955)*

103 Kain ZN, Caldwell-Andrews AA. Preoperative Psychological Preparation of the Child for Surgery: An Update. *Anesthesiology Clinics of North America*. 2005; 23(4):597-614. *(Guideline Ref ID 480)*

104 Kain ZN, Caldwell-Andrews AA, Krivutza DM, Weinberg ME, Gaal D, Wang SM, Mayes LC. Interactive Music Therapy As a Treatment for Preoperative Anxiety in Children: a Randomized Controlled Trial. *Anesthesia and Analgesia*. 2004; 98(5):1260-6, table. *(Guideline Ref ID 775)*

105 Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, Feng R, Zhang H. Preoperative Anxiety and Emergence Delirium and Postoperative Maladaptive Behaviors. *Anesthesia and Analgesia*. 2004; 99(6):1648-1654. *(Guideline Ref ID 167)*

106 Kain ZN, Caldwell-Andrews AA, Maranets I, Nelson W, Mayes LC. Predicting Which Child-Parent Pair Will Benefit From Parental Presence During Induction of Anesthesia: a Decision-Making Approach. *Anesthesia and Analgesia*. 2006; 102(1):81-84. *(Guideline Ref ID 122)*

107 Kain ZN, Caldwell-Andrews AA, Mayes LC, Wang SM, Krivutza DM, LoDolce ME. Parental Presence During Induction of Anesthesia: Physiological Effects on Parents. *Anesthesiology*. 2003; 98(1):58-64. *(Guideline Ref ID 15956)*

108 Kain ZN, Caldwell-Andrews AA, Mayes LC, Weinberg ME, Wang SM, MacLaren JE, Blount RL. Family-Centered Preparation for Surgery Improves Perioperative Outcomes in Children: a Randomized Controlled Trial. *Anesthesiology*. 2007; 106(1):65-74. *(Guideline Ref ID 15957)*

109 Kain ZN, Caldwell-Andrews AA, Wang S-M, Krivutza DM, Weinberg ME, Mayes LC. Parental Intervention Choices for Children Undergoing Repeated Surgeries. *Anesthesia and Analgesia*. 2003; 96(4):970-975. *(Guideline Ref ID 935)*

110 Kain ZN, Caramico LA, Mayes LC, Genevro JL, Bornstein MH, Hofstadter MB. Preoperative Preparation Programs in Children: a Comparative Examination. *Anesthesia and Analgesia*. 1998; 87(6):1249-1255. *(Guideline Ref ID 328)*

111 Kain ZN, Ferris CA, Mayes LC, Rimar S. Parental Presence During Induction of Anaesthesia: Practice Differences Between the United States and Great Britain. *Paediatric Anaesthesia*. 1996; 6(3):187-193. *(Guideline Ref ID 386)*

112 Kain ZN, MacLaren J, Weinberg M, Huszti H, Anderson C, Mayes L. How Many Parents Should We Let into the Operating Room? *Paediatric Anaesthesia*. 2009; 19(3):244-249. *(Guideline Ref ID 622)*

113 Kain ZN, Mayes LC, Caldwell-Andrews AA, Alexander GM, Krivutza D, Teague BA, Wang S-M. Sleeping Characteristics of Children Undergoing Outpatient Elective Surgery. *Anesthesiology*. 2002; 97(5):1093-1101. *(Guideline Ref ID 949)*

114 Kain ZN, Mayes LC, Caldwell-Andrews AA, Saadat H, McClain B, Wang S-M. Predicting Which Children Benefit Most From Parental Presence During Induction of Anesthesia. *Paediatric Anaesthesia*. 2006; 16(6):627-634. *(Guideline Ref ID 790)*

115 Kain ZN, Mayes LC, Caramico LA. Preoperative Preparation in Children: a Cross-Sectional Study. *Journal of Clinical Anesthesia*. 1996; 8(6):508-514. *(Guideline Ref ID 15970)*

116 Kain ZN, Mayes LC, Caramico LA, Silver D, Spieker M, Nygren MM, Anderson G, Rimar S. Parental Presence During Induction of Anesthesia. A Randomized Controlled Trial. *Anesthesiology*. 1996; 84(5):1060-1067. *(Guideline Ref ID 15884)*

117 Kain ZN, Mayes LC, Cicchetti DV, Bagnall AL, Finley JD, Hofstadter MB. The Yale Preoperative Anxiety Scale: How Does It Compare With a "Gold Standard"? *Anesthesia and Analgesia*. 1997; 85(4):783-788. *(Guideline Ref ID 15981)*

118 Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB. Parental Presence During Induction of Anesthesia Versus Sedative Premedication: Which Intervention Is More Effective? *Anesthesiology*. 1998; 89(5):1147-1156. *(Guideline Ref ID 865)*

119 Kain ZN, Mayes LC, Wang SM, Caramico LA, Krivutza DM, Hofstadter MB. Parental Presence and a Sedative Premedicant for Children Undergoing Surgery: a Hierarchical Study. *Anesthesiology*. 2000; 92(4):939-946. *(Guideline Ref ID 175)*

120 Kain ZN, Wang SM, Caramico LA, Hofstadter M, Mayes LC. Parental Desire for Perioperative Information and Informed Consent: a Two-Phase Study. *Anesthesia and Analgesia*. 1997; 84(2):299-306. *(Guideline Ref ID 369)*

121 Kain ZN, Wang SM, Mayes LC, Krivutza DM, Teague BA. Sensory Stimuli and Anxiety in Children Undergoing Surgery: a Randomized, Controlled Trial. *Anesthesia and Analgesia*. 2001; 92(4):897-903. *(Guideline Ref ID 284)*

122 Kain ZN, Mayes LC. Anxiety in Children During the Perioperative Period. In: Bornstein MH, Genevro JL (eds), *Child Development and Behavioral Pediatrics*, Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers, 1996: 85-103. *(Guideline Ref ID 16009)*

123 Kam PC, Voss TJ, Gold PD, Pitkin J. Behaviour of Children Associated With Parental Participation During Induction of General Anaesthesia. *Journal of Paediatrics and Child Health*. 1998; 34(1):29-31. *(Guideline Ref ID 15887)*

124 Kanegaye JT, Favela JL, Acosta M, Bank DE. High-Dose Rectal Midazolam for Pediatric Procedures: a Randomized Trial of Sedative Efficacy and Agitation. *Pediatric Emergency Care*. 2003; 19(5):329-336. *(Guideline Ref ID 601)*

125 Kapur A, Chawla SH, Goyal A, Gauba K, Bhardwaj N. Efficacy and Acceptabilty of Oral-Transmucosal Midazolam As a Conscious Sedation Agent in Pre-School Children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*. 2004; 22(3):109-113. *(Guideline Ref ID 455)*

126 Katz ER, Kellerman J, Siegel SE. Behavioral Distress in Children With Cancer Undergoing Medical Procedures: Developmental Considerations. *Journal of Consulting and Clinical Psychology*. 1980; 48(3):356-365. *(Guideline Ref ID 4329)*

127 Kazak AE, Penati B, Waibel MK, Blackall GF. The Perception of Procedures Questionnaire: Psychometric Properties of a Brief Parent Report Measure of Procedural Distress. *Journal of Pediatric Psychology*. 1996; 21(2):195-207. *(Guideline Ref ID 15997)*

128 Keidan I, Gozal D, Minuskin T, Weinberg M, Barkaly H, Augarten A. The Effect of Fasting Practice on Sedation With Chloral Hydrate. *Pediatric Emergency Care*. 2004; 20(12):805-807. *(Guideline Ref ID 76)*

129 Kennedy RM, Porter FL, Miller JP, Jaffe DM. Comparison of Fentanyl/Midazolam With Ketamine/Midazolam for Pediatric Orthopedic Emergencies. *Pediatrics*. 1998; 102(4 Pt 1):956-963. *(Guideline Ref ID 1014)*

130 Kolk AM, van HR, Fiedeldij Dop MJ. Preparing Children for Venepuncture. The Effect of an Integrated Intervention on Distress Before and During Venepuncture. *Child: Care, Health and Development*. 2000; 26(3):251-260. *(Guideline Ref ID 15962)*

131 Krauss B, Green SM. Procedural Sedation and Analgesia in Children. *Lancet*. 2006; 367(9512):766-780. *(Guideline Ref ID 3956)*

132 Kriwanek KL, Wan J, Beaty JH, Pershad J. Axillary Block for Analgesia During Manipulation of Forearm Fractures in the Pediatric Emergency Department a Prospective Randomized Comparative Trial. *Journal of Pediatric Orthopedics*. 2006; 26(6):737-740. *(Guideline Ref ID 206)*

133 Kupietzky A, Tal E, Shapira J, Ram D. Fasting State and Episodes of Vomiting in Children Receiving Nitrous Oxide for Dental Treatment. *Pediatric Dentistry*. 2008; 30(5):414-419. *(Guideline Ref ID 15936)*

134 Lahoud GY, Averley PA. Comparison of Sevoflurane and Nitrous Oxide Mixture With Nitrous Oxide Alone for Inhalation Conscious Sedation in Children Having Dental Treatment: a Randomised Controlled Trial. *Anaesthesia*. 2002; 57(5):446-450. *(Guideline Ref ID 739)*

135 Larsen R, Galloway D, Wadera S, Kjar D, Hardy D, Mirkes C, Wick L, Pohl JF. Safety of Propofol Sedation for Pediatric Outpatient Procedures. *Clinical Pediatrics*. 2009; 48(8):819-823. *(Guideline Ref ID 2783)*

136 Layangool T, Sangtawesin C, Kirawittaya T, Prompan W, Attachoo A, Pechdamrongsakul A, Intasorn Y, Hanchai P, Ounjareon C, Noisang P. A Comparison of Oral Chloral Hydrate and Sublingual Midazolam Sedation for Echocardiogram in Children. *Journal of the Medical Association of Thailand*. 2008; 91 Suppl 3:S45-S52. *(Guideline Ref ID 4388)*

137 Lee JY, Vann WF, Roberts MW. A Cost Analysis of Treating Pediatric Dental Patients Using General Anesthesia Versus Conscious Sedation. *Pediatric Dentistry*. 2000; 22:27-32. *(Guideline Ref ID 4214)*

138 Lee-Kim SJ, Fadavi S, Punwani I, Koerber A. Nasal Versus Oral Midazolam Sedation for Pediatric Dental Patients. *Journal of Dentistry for Children*. 2004; 71(2):126-130. *(Guideline Ref ID 454)*

139 Lewis Claar R., Walker LS, Barnard JA. Children's Knowledge, Anticipatory Anxiety, Procedural Distress, and Recall of Esophagogastroduodenoscopy. *Journal of Pediatric Gastroenterology and Nutrition*. 2002; 34(1):68-72. *(Guideline Ref ID 256)*

140 Liacouras CA, Mascarenhas M, Poon C, Wenner WJ. Placebo-Controlled Trial Assessing the Use of Oral Midazolam As a Premedication to Conscious Sedation for Pediatric Endoscopy. *Gastrointestinal Endoscopy*. 1998; 47(6):455-460. *(Guideline Ref ID 1029)*

141 Lightdale JR, Mahoney LB, Fredette ME, Valim C, Wong S, DiNardo JA. Nurse Reports of Adverse Events During Sedation Procedures at a Pediatric Hospital. *Journal of Perianesthesia Nursing*. 2009; 24(5):300-306. *(Guideline Ref ID 2801)*

142 Liossi C, Franck L. Psychological Interventions for Acute Pediatric Pain. In: Macintyre P, Rowbotham D, Walker S (eds), *Clinical Pain Management - Acute Pain*, 2nd edn. Hodder Arnold, 2008: 308-323. *(Guideline Ref ID 16011)*

143 Liossi C, Hatira P. Clinical Hypnosis Versus Cognitive Behavioral Training for Pain Management With Pediatric Cancer Patients Undergoing Bone Marrow Aspirations. *International Journal of Clinical and Experimental Hypnosis*. 1999; 47(2):104-116. *(Guideline Ref ID 15998)*

144 Liossi C, Hatira P. Clinical Hypnosis in the Alleviation of Procedure-Related Pain in Pediatric Oncology Patients. *International Journal of Clinical and Experimental Hypnosis*. 2003; 51(1):4-28. *(Guideline Ref ID 15999)*

145 Liossi C, White P, Franck L, Hatira P. Parental Pain Expectancy As a Mediator Between Child Expected and Experienced Procedure-Related Pain Intensity During Painful Medical Procedures. *Clinical Journal of Pain*. 2007; 23(5):392-399. *(Guideline Ref ID 16001)*

146 Liossi C, White P, Hatira P. Randomized Clinical Trial of Local Anesthetic Versus a Combination of Local Anesthetic With Self-Hypnosis in the Management of Pediatric Procedure-Related Pain. *Health Psychology*. 2006; 25(3):307-315. *(Guideline Ref ID 16000)*

147 Liossi C, White P, Hatira P. A Randomized Clinical Trial of a Brief Hypnosis Intervention to Control Venepuncture-Related Pain of Paediatric Cancer Patients. *Pain*. 2009; 142(3):255-263. *(Guideline Ref ID 617)*

148 Litman RS, Perkins FM, Dawson SC. Parental Knowledge and Attitudes Toward Discussing the Risk of Death From Anesthesia. *Anesthesia and Analgesia*. 1993; 77(2):256-260. *(Guideline Ref ID 15974)*

149 Ljungman G, Kreuger A, Andreasson S, Gordh T, Sorensen S. Midazolam Nasal Spray Reduces Procedural Anxiety in Children. *Pediatrics*. 2000; 105(1 Pt 1):73-78. *(Guideline Ref ID 902)*

150 Loewy J, Hallan C, Friedman E, Martinez C. Sleep/Sedation in Children Undergoing EEG Testing: a Comparison of Chloral Hydrate and Music Therapy. *Journal of Perianesthesia Nursing*. 2005; 20(5):323-332. *(Guideline Ref ID 3050)*

151 Lucas da Silva PS, Oliveira Iglesias SB, Leao FV, Aguiar VE, Brunow dC. Procedural Sedation for Insertion of Central Venous Catheters in Children: Comparison of Midazolam/Fentanyl With Midazolam/Ketamine. *Paediatric Anaesthesia*. 2007; 17(4):358-363. *(Guideline Ref ID 153)*

152 Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM. A Randomized Clinical Trial of Continuous-Flow Nitrous Oxide and Midazolam for Sedation of Young Children During Laceration Repair. *Annals of Emergency Medicine*. 2001; 37(1):20-27. *(Guideline Ref ID 824)*

153 Luhmann JD, Schootman M, Luhmann SJ, Kennedy RM. A Randomized Comparison of Nitrous Oxide Plus Hematoma Block Versus Ketamine Plus Midazolam for Emergency Department Forearm Fracture Reduction in Children. *Pediatrics*. 2006; 118(4):e1078-e1086. *(Guideline Ref ID 220)*

154 Lumley MA, Melamed BG, Abeles LA. Predicting Children's Presurgical Anxiety and Subsequent Behavior Changes. *Journal of Pediatric Psychology*. 1993; 18(4):481-497. *(Guideline Ref ID 15896)*

155 Mahajan L, Wyllie R, Steffen R, Kay M, Kitaoka G, Dettorre J, Sarigol S, Mccue K. The Effects of a Psychological Preparation Program on Anxiety in Children and Adolescents Undergoing Gastrointestinal Endoscopy. *Journal of Pediatric Gastroenterology and Nutrition*. 1998; 27(2):161-165. *(Guideline Ref ID 645)*

156 Malviya S, Voepel-Lewis T, Prochaska G, Tait AR. Prolonged Recovery and Delayed Side Effects of Sedation for Diagnostic Imaging Studies in Children. *Pediatrics*. 2000; 105(3):E42. *(Guideline Ref ID 35)*

157 Mamula P, Markowitz JE, Neiswender K, Zimmerman A, Wood S, Garofolo M, Nieberle M, Trautwein A, Lombardi S, Sargent-Harkins L, Lachewitz G, Farace L, Morgan V, Puma A, Cook-Sather SD, Liacouras CA. Safety of Intravenous Midazolam and Fentanyl for Pediatric GI Endoscopy: Prospective Study of 1578 Endoscopies. *Gastrointestinal Endoscopy*. 2007; 65(2):203-210. *(Guideline Ref ID 16)*

158 Margolis JO, Ginsberg B, Dear GL, Ross AK, Goral JE, Bailey AG. Paediatric Preoperative Teaching: Effects at Induction and Postoperatively. *Paediatric Anaesthesia*. 1998; 8(1):17-23. *(Guideline Ref ID 15899)*

159 Marti-Bonmati L, Ronchera-Oms CL, Casillas C, Poyatos C, Torrijo C, Jimenez NV. Randomised Double-Blind Clinical Trial of Intermediate- Versus High-Dose Chloral Hydrate for Neuroimaging of Children. *Neuroradiology*. 1995; 37(8):687-691. *(Guideline Ref ID 1204)*

160 Martinez JL, Sutters KA, Waite S, Davis J, Medina E, Montano N, Merzel D, Marquez C. A Comparison of Oral Diazepam Versus Midazolam, Administered With Intravenous Meperidine, As Premedication to Sedation for Pediatric Endoscopy. *Journal of Pediatric Gastroenterology and Nutrition*. 2002; 35(1):51-58. *(Guideline Ref ID 717)*

161 McCann W, Wilson S, Larsen P, Stehle B. The Effects of Nitrous Oxide on Behavior and Physiological Parameters During Conscious Sedation With a Moderate Dose of Chloral Hydrate and Hydroxyzine. *Pediatric Dentistry*. 1996; 18(1):35-41. *(Guideline Ref ID 1195)*

162 McEwen A, Moorthy C, Quantock C, Rose H, Kavanagh R. The Effect of Videotaped Preoperative Information on Parental Anxiety During Anesthesia Induction for Elective Pediatric Procedures. *Paediatric Anaesthesia*. 2007; 17(6):534-539. *(Guideline Ref ID 83)*

163 McGlone RG, Howes MC, Joshi M. The Lancaster Experience of 2.0 to 2.5 Mg/Kg Intramuscular Ketamine for Paediatric Sedation: 501 Cases and Analysis. *Emergency Medicine Journal*. 2004; 21(3):290-295. *(Guideline Ref ID 47)*

164 McQueen A, Wright RO, Kido MM, Kaye E, Krauss B. Procedural Sedation and Analgesia Outcomes in Children After Discharge From the Emergency Department:

Ketamine Versus Fentanyl/Midazolam. *Annals of Emergency Medicine*. 2009; 54(2):191-197. *(Guideline Ref ID 4351)*

165 Megel ME, Heser R, Matthews K. Parents' Assistance to Children Having Immunizations. *Issues in Comprehensive Pediatric Nursing*. 2002; 25(3):151-165. *(Guideline Ref ID 15965)*

166 Melamed BG, Yurcheson R, Fleece EL, Hutcherson S, Hawes R. Effects of Film Modeling on the Reduction of Anxiety-Related Behaviors in Individuals Varying in Level of Previous Experience in the Stress Situation. *Journal of Consulting and Clinical Psychology*. 1978; 46(6):1357-1367. *(Guideline Ref ID 15963)*

167 Melamed BG, Meyer R, Gee C, Soule L. The Influence of Time and Type of Preparation on Children's Adjustement to Hospitalization. *Journal of Pediatric Psychology*. 1976; 1(4):31-37. *(Guideline Ref ID 15951)*

168 Merola C, Albarracin C, Lebowitz P, Bienkowski RS, Barst SM. An Audit of Adverse Events in Children Sedated With Chloral Hydrate or Propofol During Imaging Studies. *Paediatric Anaesthesia*. 1995; 5(6):375-378. *(Guideline Ref ID 110)*

169 Moore PA, Mickey EA, Hargreaves JA, Needleman HL. Sedation in Pediatric Dentistry: a Practical Assessment Procedure. *Journal of the American Dental Association*. 1984; 109(4):564-569. *(Guideline Ref ID 1703)*

170 Mortazavi M, Pourhashemi SJ, Khosravi MB, Ashtari S, Ghaderi F. Assessment of a Low Dose of IV Midazolam Used Orally for Conscious Sedation in Pediatric Dentistry. *Daru*. 2009; 17(2):79-82. *(Guideline Ref ID 2777)*

171 Napoli KL, Ingall CG, Martin GR. Safety and Efficacy of Chloral Hydrate Sedation in Children Undergoing Echocardiography. *Journal of Pediatrics*. 1996; 129(2):287-291. *(Guideline Ref ID 44)*

172 National Institute for Health and Clinical Excellence. *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence; 2009. *(Guideline Ref ID 15983)*

173 Needleman HL, Joshi A, Griffith DG. Conscious Sedation of Pediatric Dental Patients Using Chloral Hydrate, Hydroxyzine, and Nitrous Oxide--a Retrospective Study of 382 Sedations. *Pediatric Dentistry*. 1995; 17(7):424-431. *(Guideline Ref ID 45)*

174 O'Byrne KK, Peterson L, Saldana L. Survey of Pediatric Hospitals' Preparation Programs: Evidence of the Impact of Health Psychology Research. *Health Psychology*. 1997; 16(2):147-154. *(Guideline Ref ID 15977)*

175 Olumide F, Newton JT, Dunne S, Gilbert DB. Anticipatory Anxiety in Children Visiting the Dentist: Lack of Effect of Preparatory Information. *International Journal of Paediatric Dentistry*. 2009; 19(5):338-342. *(Guideline Ref ID 15940)*

176 Oxman AD, Cook DJ, Guyatt GH. Users' Guides to the Medical Literature: VI. How to Use an Overview. *Journal of the American Medical Association*. 1994; 272(17):1367-1371. *(Guideline Ref ID 15735)*

177 Palermo TM, Tripi PA, Burgess E. Parental Presence During Anaesthesia Induction for Outpatient Surgery of the Infant. *Paediatric Anaesthesia*. 2000; 10(5):487-491. *(Guideline Ref ID 1013)*

178 Paspatis GA, Charoniti I, Manolaraki M, Vardas E, Papanikolaou N, Anastasiadou A, Gritzali A. Synergistic Sedation With Oral Midazolam As a Premedication and Intravenous Propofol Versus Intravenous Propofol Alone in Upper Gastrointestinal Endoscopies in Children: a Prospective, Randomized Study. *Journal of Pediatric Gastroenterology and Nutrition*. 2006; 43(2):195-199. *(Guideline Ref ID 239)*

179 Patel A, Schieble T, Davidson M, Tran MC, Schoenberg C, Delphin E, Bennett H. Distraction With a Hand-Held Video Game Reduces Pediatric Preoperative Anxiety. *Paediatric Anaesthesia*. 2006; 16(10):1019-1027. *(Guideline Ref ID 8332)*

180 Peña BMG, Krauss B. Adverse Events of Procedural Sedation and Analgesia in a Pediatric Emergency Department. *Annals of Emergency Medicine*. 1999; 34(4 I):483-491. *(Guideline Ref ID 384)*

181 Pershad J, Todd K, Waters T. Cost-Effectiveness Analysis of Sedation and Analgesia Regimens During Fracture Manipulation in the Pediatric Emergency Department. *Pediatric Emergency Care*. 2006; 22:729-736. *(Guideline Ref ID 3745)*

182 Peterson L. Coping by Children Undergoing Stressful Medical Procedures: Some Conceptual, Methodological, and Therapeutic Issues. *Journal of Consulting and Clinical Psychology*. 1989; 57(3):380-387. *(Guideline Ref ID 15967)*

183 Piira T, Sugiura T, Champion GD, Donnelly N, Cole ASJ. The Role of Parental Presence in the Context of Children's Medical Procedures: A Systematic Review. *Child: Care, Health and Development*. 2005; 31(2):233-243. *(Guideline Ref ID 860)*

184 Pitetti RD, Singh S, Pierce MC. Safe and Efficacious Use of Procedural Sedation and Analgesia by Nonanesthesiologists in a Pediatric Emergency Department. *Archives of Pediatrics and Adolescent Medicine*. 2003; 157(11):1090-1096. *(Guideline Ref ID 304)*

185 Power N, Liossi C, Franck LS. Family-Centered Care. Helping Parents to Help Their Child With Procedural and Everyday Pain: Practical, Evidence-Based Advice. *Journal for Specialists in Pediatric Nursing*. 2007; 12(3):203-209. *(Guideline Ref ID 16008)*

186 Press J, Gidron Y, Maimon M, Gonen A, Goldman V, Buskila D. Effects of Active Distraction on Pain of Children Undergoing Venipuncture: Who Benefits From It? *Pain Clinic*. 2003; 15(3):261-269. *(Guideline Ref ID 16006)*

187 Primosch RE, Buzzi IM, Jerrell G. Effect of Nitrous Oxide-Oxygen Inhalation With Scavenging on Behavioral and Physiological Parameters During Routine Pediatric Dental Treatment. *Pediatric Dentistry*. 1999; 21(7):417-420. *(Guideline Ref ID 965)*

188 Ramaswamy P. Pediatric Procedural Sedation With Ketamine: Time to Discharge After Intramuscular Versus Intravenous Administration. *Academic Emergency Medicine*. 2009; 16(2):101-107. *(Guideline Ref ID 120)*

189 Reeves ST, Wiedenfeld KR, Wrobleski J, Hardin CL, Pinosky ML. A Randomized Double-Blind Trial of Chloral Hydrate/Hydroxyzine Versus Midazolam/Acetaminophen in the Sedation of Pediatric Dental Outpatients. *Journal of Dentistry for Children*. 1996; 63(2):95-100. *(Guideline Ref ID 1182)*

190 Roback MG, Bajaj L, Wathen JE, Bothner J. Preprocedural Fasting and Adverse Events in Procedural Sedation and Analgesia in a Pediatric Emergency Department: Are They Related? *Annals of Emergency Medicine*. 2004; 44(5):454-459. *(Guideline Ref ID 4325)*

191 Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse Events Associated With Procedural Sedation and Analgesia in a Pediatric Emergency Department: a Comparison of Common Parenteral Drugs. *Academic Emergency Medicine*. 2005; 12(6):508-513. *(Guideline Ref ID 33)*

192 Roback MG, Wathen JE, MacKenzie T, Bajaj L. A Randomized, Controlled Trial of I.v. Versus I.m. Ketamine for Sedation of Pediatric Patients Receiving Emergency Department Orthopedic Procedures. *Annals of Emergency Medicine*. 2006; 48(5):605-612. *(Guideline Ref ID 212)*

193 Robinson PJ, Kobayashi K. Development and Evaluation of a Presurgical Preparation Program. *Journal of Pediatric Psychology*. 1991; 16(2):193-212. *(Guideline Ref ID 15978)*

194 Ronchera-Oms CL, Casillas C, Marti-Bonmati L, Poyatos C, Tomas J, Sobejano A, Jimenez NV. Oral Chloral Hydrate Provides Effective and Safe Sedation in Paediatric Magnetic Resonance Imaging. *Journal of Clinical Pharmacy and Therapeutics*. 1994; 19(4):239-243. *(Guideline Ref ID 8314)*

195 Rosen S, Svensson M, Nilsson U. Calm or Not Calm: the Question of Anxiety in the Perianesthesia Patient. *Journal of Perianesthesia Nursing*. 2008; 23(4):237-246. *(Guideline Ref ID 15907)*

196 Royal College of Anaesthetists and Royal College of Radiologists. *Sedation and Anaesthesia in Radiology. Report of a Joint Working Party*. London: Royal College of Radiologists; 1992. *(Guideline Ref ID 16023)*

197 Sacchetti A, Senula G, Strickland J, Dubin R. Procedural Sedation in the Community Emergency Department: Initial Results of the ProSCED Registry. *Academic Emergency Medicine*. 2007; 14(1):41-46. *(Guideline Ref ID 4335)*

198 Sanborn PA, Michna E, Zurakowski D, Burrows PE, Fontaine PJ, Connor L, Mason KP. Adverse Cardiovascular and Respiratory Events During Sedation of Pediatric Patients for Imaging Examinations. *Radiology*. 2005; 237(1):288-294. *(Guideline Ref ID 42)*

199 Scherer MW, Nakamura CY. A Fear Survey Schedule for Children (FSS-FC): a Factor Analytic Comparison With Manifest Anxiety (CMAS). *Behaviour Research and Therapy*. 1968; 6(2):173-182. *(Guideline Ref ID 15994)*

200 Scottish Dental Clinical Effectiveness Programme. *Conscious Sedation in Dentistry. Dental Clinical Guidance*. Dundee: Scottish Dental Clinical Effectiveness Programme; 2006. *(Guideline Ref ID 15949)*

201 Scottish Intercollegiate Guidelines Network (SIGN). *SIGN Guideline 58: Safe Sedation of Children Undergoing Diagnostic and Therapeutic Procedures*. Edinburgh: NHS Scotland; 2002. *(Guideline Ref ID 15945)*

202 Shashikiran ND, Reddy SV, Yavagal CM. Conscious Sedation--an Artist's Science! An Indian Experience With Midazolam. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*. 2006; 24(1):7-14. *(Guideline Ref ID 275)*

203 Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does Adjunctive Midazolam Reduce Recovery Agitation After Ketamine Sedation for Pediatric

Procedures? A Randomized, Double-Blind, Placebo-Controlled Trial. *Annals of Emergency Medicine*. 2000; 35(3):229-238. *(Guideline Ref ID 897)*

204 Shirley PJ, Thompson N, Kenward M, Johnston G. Parental Anxiety Before Elective Surgery in Children. A British Perspective. *Anaesthesia*. 1998; 53(10):956-959. *(Guideline Ref ID 326)*

205 Singh N, Pandey RK, Saksena AK, Jaiswal JN. A Comparative Evaluation of Oral Midazolam With Other Sedatives As Premedication in Pediatric Dentistry. *Journal of Clinical Pediatric Dentistry*. 2002; 26(2):161-164. *(Guideline Ref ID 752)*

206 Sinha M, Christopher NC, Fenn R, Reeves L. Evaluation of Nonpharmacologic Methods of Pain and Anxiety Management for Laceration Repair in the Pediatric Emergency Department. *Pediatrics*. 2006; 117(4):1162-1168. *(Guideline Ref ID 1256)*

207 Smith L, Callery P. Children's Accounts of Their Preoperative Information Needs. *Journal of Clinical Nursing*. 2005; 14(2):230-238. *(Guideline Ref ID 15911)*

208 Standing Dental Advisory Committee (SDAC). *Conscious Sedation In The Provision of Dental Care. Report of an Expert Group on Sedation for Dentistry*. London: Department of Health; 2003. *(Guideline Ref ID 15948)*

209 Stashinko EE, Goldberger J. Test or Trauma? The Voiding Cystourethrogram Experience of Young Children. *Issues in Comprehensive Pediatric Nursing*. 1998; 21(2):85-96. *(Guideline Ref ID 15964)*

210 Suls J, Wan CK. Effects of Sensory and Procedural Information on Coping With Stressful Medical Procedures and Pain: a Meta-Analysis. *Journal of Consulting and Clinical Psychology*. 1989; 57(3):372-379. *(Guideline Ref ID 15968)*

211 Tak JH, van Bon WH. Pain- and Distress-Reducing Interventions for Venepuncture in Children. *Child: Care, Health and Development*. 2006; 32(3):257-268. *(Guideline Ref ID 15973)*

212 Theroux MC, West DW, Corddry DH, Hyde PM, Bachrach SJ, Cronan KM, Kettrick RG. Efficacy of Intranasal Midazolam in Facilitating Suturing of Lacerations in Preschool Children in the Emergency Department. *Pediatrics*. 1993; 91(3):624-627. *(Guideline Ref ID 1393)*

213 Thompson JR, Schneider S, Ashwal S, Holden BS, Hinshaw DB, Jr., Hasso AN. The Choice of Sedation for Computed Tomography in Children: a Prospective Evaluation. *Radiology*. 1982; 143(2):475-479. *(Guideline Ref ID 1739)*

214 Thorp AW, Brown L, Green SM. Ketamine-Associated Vomiting: Is It Dose-Related? *Pediatric Emergency Care*. 2009; 25(1):15-18. *(Guideline Ref ID 442)*

215 Tosun Z, Aksu R, Guler G, Esmaoglu A, Akin A, Aslan D, Boyaci A. Propofol-Ketamine Vs Propofol-Fentanyl for Sedation During Pediatric Upper Gastrointestinal Endoscopy. *Paediatric Anaesthesia*. 2007; 17(10):983-988. *(Guideline Ref ID 97)*

216 Train H, Colville G, Allan R, Thurlbeck S. Paediatric 99mTc-DMSA Imaging: Reducing Distress and Rate of Sedation Using a Psychological Approach. *Clinical Radiology*. 2006; 61(10):868-874. *(Guideline Ref ID 8336)*

217 Treston G. Prolonged Pre-Procedure Fasting Time Is Unnecessary When Using Titrated Intravenous Ketamine for Paediatric Procedural Sedation. *Emergency Medicine Australasia*. 2004; 16(2):145-150. *(Guideline Ref ID 15926)*

218 Treston G, Bell A, Cardwell R, Fincher G, Chand D, Cashion G. What Is the Nature of the Emergence Phenomenon When Using Intravenous or Intramuscular Ketamine for Paediatric Procedural Sedation?: Paediatric Emergency Medicine. *Emergency Medicine Australasia*. 2009; 21(4):315-322. *(Guideline Ref ID 4502)*

219 Uman LS, Chambers CT, McGrath PJ, Kisely S. Psychological Interventions for Needle-Related Procedural Pain and Distress in Children and Adolescents. *Cochrane Database of Systematic Reviews*. 2006;(4):CD005179. *(Guideline Ref ID 15958)*

220 Vagnoli L, Caprilli S, Robiglio A, Messeri A. Clown Doctors As a Treatment for Preoperative Anxiety in Children: a Randomized, Prospective Study. *Pediatrics*. 2005; 116(4):e563-e567. *(Guideline Ref ID 15912)*

221 Vardi A, Salem Y, Padeh S, Paret G, Barzilay Z. Is Propofol Safe for Procedural Sedation in Children? A Prospective Evaluation of Propofol Versus Ketamine in Pediatric Critical Care. *Critical Care Medicine*. 2002; 30(6):1231-1236. *(Guideline Ref ID 724)*

222 Veerkamp JS, Gruythuysen RJ, Hoogstraten J, van Amerongen WE. Anxiety Reduction With Nitrous Oxide: a Permanent Solution? *Journal of Dentistry for Children*. 1995; 62(1):44-48. *(Guideline Ref ID 1245)*

223 Veerkamp JS, Gruythuysen RJ, van Amerongen WE, Hoogstraten J. Dental Treatment of Fearful Children Using Nitrous Oxide. Part 2: The Parent's Point of View. *ASDC Journal of Dentistry for Children*. 1992; 59(2):115-119. *(Guideline Ref ID 15943)*

224 Veerkamp JS, Gruythuysen RJ, van Amerongen WE, Hoogstraten J. Dental Treatment of Fearful Children Using Nitrous Oxide. Part 3: Anxiety During Sequential Visits. *Journal of Dentistry for Children*. 1993; 60(3):175-182. *(Guideline Ref ID 1367)*

225 Vernon DT, Schulman JL, Foley JM. Changes in Children's Behavior After Hospitalization. Some Dimensions of Response and Their Correlates. *American Journal of Diseases of Children*. 1966; 111(6):581-593. *(Guideline Ref ID 15995)*

226 Vespasiano M, Finkelstein M, Kurachek S. Propofol Sedation: Intensivists' Experience With 7304 Cases in a Children's Hospital. *Pediatrics*. 2007; 120(6):e1411-e1417. *(Guideline Ref ID 149)*

227 Waisel DB, Truog RD. The Benefits of the Explanation of the Risks of Anesthesia in the Day Surgery Patient. *Journal of Clinical Anesthesia*. 1995; 7(3):200-204. *(Guideline Ref ID 15975)*

228 Wang SM, Maranets I, Weinberg ME, Caldwell-Andrews AA, Kain ZN. Parental Auricular Acupuncture As an Adjunct for Parental Presence During Induction of Anesthesia. *Anesthesiology*. 2004; 100(6):1399-1404. *(Guideline Ref ID 15976)*

229 Wathen JE, Roback MG, MacKenzie T, Bothner JP. Does Midazolam Alter the Clinical Effects of Intravenous Ketamine Sedation in Children? A Double-Blind, Randomized, Controlled, Emergency Department Trial. *Annals of Emergency Medicine*. 2000; 36(6):579-588. *(Guideline Ref ID 845)*

230 Watson AT, Visram A. Children's Preoperative Anxiety and Postoperative Behaviour. *Paediatric Anaesthesia*. 2003; 13(3):188-204. *(Guideline Ref ID 933)*

231 Wilson KE, Girdler NM, Welbury RR. Randomized, Controlled, Cross-Over Clinical Trial Comparing Intravenous Midazolam Sedation With Nitrous Oxide Sedation in Children Undergoing Dental Extractions. *British Journal of Anaesthesia*. 2003; 91(6):850-856. *(Guideline Ref ID 589)*

232 Wilson KE, Girdler NM, Welbury RR. A Comparison of Oral Midazolam and Nitrous Oxide Sedation for Dental Extractions in Children. *Anaesthesia*. 2006; 61(12):1138-1144. *(Guideline Ref ID 204)*

233 Wilson KE, Welbury RR, Girdler NM. A Randomised, Controlled, Crossover Trial of Oral Midazolam and Nitrous Oxide for Paediatric Dental Sedation. *Anaesthesia*. 2002; 57(9):860-867. *(Guideline Ref ID 711)*

234 Wilson KE, Welbury RR, Girdler NM. A Study of the Effectiveness of Oral Midazolam Sedation for Orthodontic Extraction of Permanent Teeth in Children: a Prospective, Randomised, Controlled, Crossover Trial. *British Dental Journal*. 2002; 192(8):457-462. *(Guideline Ref ID 729)*

235 Wilson KE, Welbury RR, Girdler NM. Comparison of Transmucosal Midazolam With Inhalation Sedation for Dental Extractions in Children. A Randomized, Cross-Over, Clinical Trial. *Acta Anaesthesiologica Scandinavica*. 2007; 51(8):1062-1067. *(Guideline Ref ID 111)*

236 Wright KD, Stewart SH, Finley GA, Buffett-Jerrott SE. Prevention and Intervention Strategies to Alleviate Preoperative Anxiety in Children: A Critical Review. *Behavior Modification*. 2007; 31(1):52-79. *(Guideline Ref ID 8338)*

237 Yip P, Middleton P, Cyna AM, Carlyle AV. Non-Pharmacological Interventions for Assisting the Induction of Anaesthesia in Children. *Cochrane Database of Systematic Reviews*. 2009;(3):CD006447. *(Guideline Ref ID 1733)*

238 Zastrow C, Navarre R. Nominal Group - New Tool for Making Social-Work Education Relevant. *Journal of Education for Social Work*. 1977; 13(1):112-118. *(Guideline Ref ID 15750)*

239 Zier JL, Rivard PF, Krach LE, Wendorf HR. Effectiveness of Sedation Using Nitrous Oxide Compared With Enteral Midazolam for Botulinum Toxin A Injections in Children. *Developmental Medicine and Child Neurology*. 2008; 50(11):854-858. *(Guideline Ref ID 4328)*

240 Zuwala R, Barber KR. Reducing Anxiety in Parents Before and During Pediatric Anesthesia Induction. *AANA Journal*. 2001; 69(1):21-25. *(Guideline Ref ID 264)*

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