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Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial

RA Elliott
K Payne
JK Moore
LM Davies
NJN Harper
AS St. Leger
E Moore
GMM Thoms
BJ Pollard
GA McHugh
J Bennett
G Lawrence
J Kerr

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Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial

RA Elliott[1*]
K Payne[1]
JK Moore[2]
LM Davies[3]
NJN Harper[4]
AS St. Leger[5]
EW Moore[2]
GMM Thoms[4]
BJ Pollard[4]
GA McHugh[6]
J Bennett[1]
G Lawrence[1]
J Kerr[2]

[1] School of Pharmacy & Pharmaceutical Sciences, University of Manchester, UK
[2] Department of Anaesthesia, Wirral NHS Trust, Upton, UK
[3] School of Psychiatry & Behavioural Sciences, University of Manchester, UK
[4] Department of Anaesthesia, Central Manchester & Manchester Children's University Hospitals NHS Trust, UK
[5] School of Epidemiology & Health Sciences, University of Manchester, UK
[6] School of Nursing, Midwifery & Health Visiting, University of Manchester, UK

[*] Corresponding author

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NHS R&D HTA Programme

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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Contents

List of abbreviations

ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
CESA	cost-effectiveness study in anaesthesia
CFQ	Cognitive Failure Questionnaire
CI	confidence interval
CV	contingent valuation
df	degrees of freedom
D&C	dilatation and curettage
DSST	Digit Symbol Substitution Test
ENT	ear, nose and throat
GHQ	General Health Questionnaire
GP	general practitioner
ICER	incremental cost-effectiveness ratio
i.m.	intramuscular
IPPV	intermittent positive pressure ventilation
IUD	intrauterine device
i.v.	intravenous
LMA	laryngeal mask airway
MAC	minimum alveolar concentration
MACL	Mood Adjective Checklist
MIR	minimum infusion rate
NA	not available
NEC	not elsewhere classified
N_2O	nitrous oxide
NS	not significant
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAT	Perceptive Accuracy Test
PHBQ	Post Hospital Behaviour Questionnaire
PONV	postoperative nausea and vomiting
QALY	quality-adjusted life-year
QoR-40	quality of recovery score
RCT	randomised controlled trial
RRR	relative risk reduction
SD	standard deviation
SF-36	Short Form with 36 items
STAI	State–Trait Anxiety Inventory
TAS	Tactile Scale
TIVA	total intravenous anaesthesia
TPPPS	Toddler–Preschooler Postoperative Pain Scale
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The aim of the project was to provide robust evidence on the relative costs, patient benefits and acceptability of different anaesthetic agents, by assessing the relative cost-effectiveness of different anaesthetic agents in adult and paediatric patients undergoing day surgery.

Objectives

The objectives were to identify and value resource use, impact on patients and relative value for money associated with different anaesthetic agents in day surgery.

Methods

The study consisted of three parts:

- A literature review of clinical outcomes, patient-based outcomes and economic data.
- A national survey of 270 anaesthetists (October 2000) to determine anaesthetic practice in adult and paediatric day surgery.
- A prospective randomised controlled trial (RCT) to compare the cost-effectiveness of anaesthetic regimens (CESA). The trial was carried out at St. Mary's Hospital, Manchester, and at Arrowe Park and Clatterbridge Hospitals, Wirral. The sample comprised adult general, orthopaedic and gynaecology patients, and paediatric general and ear, nose and throat (ENT) patients.

Results

Literature review

The large number of RCTs available that investigated clinical outcomes involved the use of various anaesthetic combinations and approaches. There were few good comparative studies of patient-based outcomes and economic evidence. No optimal regimen was identified for adults or children on the basis of clinical outcomes, patient acceptability or efficiency.

National survey

The national survey of anaesthetists (response rate 76%) indicated the following in adult urology, adult orthopaedic and paediatric general day-case surgery, respectively:

- use of premedication, 6%, 12% and 19%
- propofol as the preferred induction agent, 78%, 81% and 51%
- isoflurane as the preferred maintenance agent, 52%, 54% and 45%
- use of prophylactic anti-emetics, 32%, 41% and 24%
- use of a laryngeal mask airway, 86%, 83% and 85%.

CESA RCT

Recruitment to the CESA RCT was 73% (adult study) and 75% (paediatric study). Ninety-five adult patients and 25 paediatric patients were withdrawn, leaving 1063 adult patients (265 propofol/propofol, 267 propofol/isoflurane, 280 propofol/sevoflurane, 251 sevoflurane/sevoflurane) and 322 paediatric patients (159 propofol/halothane, 163 sevoflurane/sevoflurane) remaining in the study until discharge. Fifteen per cent of adults and 19% of children were lost to follow-up 7 days after discharge.

Interventions (comparators)

The anaesthetics in the adult treatment arm were:

- Total intravenous anaesthesia (TIVA): propofol induction, propofol maintenance.
- Intravenous/inhalational anaesthesia (mixed): propofol induction, isoflurane/nitrous oxide (N_2O) maintenance.
- Intravenous/inhalational anaesthesia (mixed): propofol induction, sevoflurane/N_2O maintenance.
- Total inhalational anaesthesia: sevoflurane/N_2O induction, sevoflurane/N_2O maintenance.

The anaesthetics in the paediatric treatment arm were:

- Intravenous/inhalational anaesthesia: propofol induction, halothane maintenance.
- Total inhalational anaesthesia: sevoflurane/N_2O induction, sevoflurane/N_2O maintenance.

Outcome measures

Postoperative nausea and vomiting (PONV) was the primary clinical outcome measure. The contingent valuation (CV) method was used to determine patient preferences for different anaesthetic agents at day 7.

Prospective patient-based resource-use data were collected up to day 7 postdischarge, from the perspective of the NHS and the patients.

Results

Adult study

- More adults experienced PONV with sevoflurane/sevoflurane (29.9%) than with propofol/propofol (14.0%) ($p < 0.0001$), propofol/sevoflurane (16.6%) ($p < 0.001$) and propofol/isoflurane (18.2%) ($p < 0.003$).
- The length of hospital stay and total costs were not statistically different between the four study arms, but variable costs were higher in the TIVA arm and lower in the propofol/isoflurane arm.
- Of those who received intravenous induction, 79% would prefer that method in the future to inhalational induction. Of those patients who received inhalational induction, 64% would prefer that method in the future. There were no differences in the CVs for induction or maintenance between the randomisation arms.
- Propofol/propofol was the most effective and most costly. Sevoflurane/sevoflurane was the least effective, and was more costly than the mixed arms. The incremental cost-effectiveness ratio (ICER) for propofol/propofol compared with propofol/sevoflurane is £296 to avoid one PONV incident. The ICER for propofol/sevoflurane compared with propofol/isoflurane is £333 to avoid one PONV incident.
- The use of the Dion algebraic approximation for volatile anaesthetic use resulted in a 6–27% underestimation. The impact of this was strongest in the sevoflurane/sevoflurane and propofol/sevoflurane arms due to the high acquisition costs of sevoflurane.
- Investigating the use of prophylactic intravenous ondansetron 4 mg suggested that propofol/propofol would remain the most costly and effective arm. However, if this agent was used in all arms except the propofol/propofol arm, propofol/sevoflurane became the most costly and effective regimen.
- The net benefit (= total cost – (CV[induction] + CV[maintenance]) was positive in all arms and was positive for over 90% of patients. Sevoflurane/sevoflurane had a lower net benefit than did the other three arms.

Paediatric study

- More children experienced PONV with sevoflurane/sevoflurane (14.7%) than with propofol/halothane (5.7%) ($p < 0.01$).
- The length of hospital stay was not different between the randomisation arms, but variable and total costs were higher in the sevoflurane/sevoflurane arm.
- Parents whose children had not had the mask (sevoflurane) before did not want it in the future. Parents whose children had not had the injection (propofol) before did not want it in the future. The CVs for PONV avoidance were not affected by the experience of PONV.
- Propofol/halothane was more effective and less costly than the sevoflurane/sevoflurane regimen.
- In a sensitivity analysis, when isoflurane was substituted for halothane, propofol/isoflurane was more effective and less costly than sevoflurane/sevoflurane. When sevoflurane was substituted for halothane, propofol/sevoflurane was more effective and more costly than sevoflurane/sevoflurane.
- Both arms had an overall positive net benefit, and these benefits were not statistically different. The net benefit was positive for over 90% of patients in both arms.

Conclusions

The main conclusions are:

- Sevoflurane/sevoflurane is not a cost-effective regimen for day surgery in adults or children. It is associated with higher rates of PONV than propofol followed by propofol, isoflurane or sevoflurane. It is more expensive than mixed anaesthesia regimens.
- In the adult study, there were no statistically significant differences in the incidence of PONV between the regimens that used propofol for induction. However, there were statistically significant differences in the variable costs of the regimens. The propofol/isoflurane regimen was associated with the lowest cost per episode of PONV avoided.

Implications for practice

- In both adults and children a propofol-containing regimen appears to confer anti-emetic protection over a sevoflurane/sevoflurane anaesthetic regimen, without increased costs, unless TIVA is used. In children, sevoflurane/sevoflurane is also associated with agitation in recovery.

- The incidence of PONV was low despite the withholding of prophylactic anti-emetics, possibly due to the low opioid use in this study.
- The reluctance to have an inhalation induction was reduced by experience of this technique.
- Decisions around clinical practice in day surgery should not be based on inpatient evidence.
- The current development of patient information on anaesthetics needs to incorporate patients' views and preferences.

Recommendations for further research

Further research is needed in the following areas:

- the optimisation of perioperative analgesia
- routine perioperative PONV prophylaxis should be reviewed
- the risk factors for PONV
- the cost of volatile anaesthetics
- the role of patient preferences in anaesthesia.

Chapter 1
Introduction

The overall aim of this cost-effectiveness study in anaesthesia (CESA) was to provide robust evidence to healthcare professionals and policy makers about the relative costs, patient benefits and acceptability of different anaesthetic agents. This was achieved by assessing the relative cost-effectiveness of different anaesthetic agents in adult and paediatric day surgery, to provide the NHS with new and reliable information about the relative cost-effectiveness, or value for money, of the different methods of anaesthesia.

Day surgery

A surgical day patient is defined as 'a patient who is admitted for investigation or operation on a planned non-resident basis and who nonetheless requires facilities for recovery'.[1] Day surgery has grown significantly in recent years in the UK. This growth has been driven by increasing costs of inpatient care and the trend toward primary and community care, and enabled by advances in surgical and anaesthetic techniques. In 1983, 600,000 day-case procedures were performed, and by 1991 this figure had risen to 1.3 million.[2] The aim of the Royal College of Surgeons and the NHS Executive is for more than 50% of all surgery to be performed as day surgery.[1]

Operations that are acceptable for day surgery are minor or intermediate in complexity. They are normally of short duration, with the total operating time per case not exceeding 60 minutes.[1] Procedures that are suitable for day surgery are those that carry a low risk of post-operative complications.

The selection of patients who are suitable for day surgery depends on a set of criteria that include social and medical factors. There must be an adult to accompany the patient home, and the presence of an adult is required for the first 24 hours after discharge.

The patient's state of health must be assessed to determine their suitability for day surgery. Candidates for day surgery should be fit and healthy. The physical status scoring system of the American Society of Anesthesiologists (ASA) is used widely to categorise preoperative heath status.[1] ASA category I patients are healthy and category II patients have systemic disease (including disease that is well controlled with therapy) that does not interfere with normal activities. However, in certain types of surgical practice, for example urology and ophthalmology, sicker patients in ASA category III (moderate disease that limits function)[3] may be treated as day patients at the discretion of the anaesthetist.

Day-surgery anaesthesia and postanaesthetic recovery

Day surgery demands high-quality anaesthesia, maximal safety, minimal side-effects and rapid discharge. These requirements may point to local or regional anaesthesia as a first choice when feasible. However, when general anaesthesia is required, as is often the case, the characteristics of the ideal anaesthetic technique are that induction will be swift and tolerable, maintenance will be physiologically stable with readily adjustable anaesthetic depth, and the recovery phase will be rapid and complete, allowing early return to normal activities.

Developments in anaesthetic drugs have underpinned the recent growth in day surgery; and have been driven by the search for ever-better profiles of safety, side-effects and recovery. Important drugs for day-surgery anaesthesia that have been introduced within the last decade or so include the intravenous induction agent propofol and the volatile agent sevoflurane.

Recovery from general anaesthesia can be characterised as having three phases.[1] The times taken to complete each of these phases can be used as measures of the duration of action of anaesthetic agents.

- Phase 1: return of vital reflexes. This phase of recovery generally takes place in the recovery room where the patient emerges from anaesthesia. The patient can then be left unattended.
- Phase 2: recovery of bodily and psychological functions (e.g. recovery from any nausea,

dizziness or disorientation). This phase of recovery generally lasts until the patient is able to get up and walk unaided, and takes place in a ward. The patient can then return home.
- Phase 3: complete psychomotor recovery. This phase of recovery generally takes place at home. The patient can then drive, deal with household hazards and operate complex machinery safely.

During recovery, treatment may be needed for pain, or for nausea and vomiting. Postoperative pain is relieved with a range of drugs, which may be given by injection, orally or rectally. Nausea and vomiting may need treatment with anti-emetic drugs. Analgesic drugs may themselves cause nausea and vomiting.

If the patient is unfit for discharge as planned on surgical, anaesthetic or social grounds, in-patient admission is arranged. Rates of unplanned admission are used as one indicator of efficiency in day surgery.[4]

Anaesthetic practice in day surgery

Both intravenous and inhalational anaesthetic agents are used for induction and for maintenance of surgical anaesthesia.

Induction of anaesthesia

The objective is to take the patient from the conscious state into surgical anaesthesia as quickly, pleasantly and safely as possible. In most UK hospitals induction will take place in an anaesthetic room adjacent to the operating theatre. In adults, anaesthesia is most often induced using intravenous propofol, which may cause pain on injection but has a good recovery profile. In children, small veins can worsen the pain of propofol injection and children may be less accepting of intravenous needles than adults. Inhalational agents are therefore commonly used for induction in children. Intravenous or topical local anaesthetics may be used to make intravenous propofol less painful and more acceptable to patients. The traditional inhalational agent for children is halothane, which was first used in 1956, but the newer agent, sevoflurane, is rapidly gaining popularity as an induction agent.[5–7]

Intubation

Immediately following induction of anaesthesia, endotracheal intubation may be needed for airway management; either because artificial ventilation is required, or to prevent regurgitation and aspiration of gastric contents into the lungs. In some kinds of surgery there may be several indications to intubate the trachea. For example, in gynaecological laparoscopy there is a steep head-down tilt and gas insufflated by the surgeon raises the pressure in the abdomen, compromising ventilation and increasing the risk of gastric reflux.[8] Muscle relaxants (e.g. suxamethonium, vecuronium, atracurium, mivacurium) are administered intravenously to make intubation possible.[9]

When intubation of the trachea is not needed, the airway will usually be managed using a laryngeal mask airway, which does not necessitate giving muscle-relaxing drugs.[10] The laryngeal mask airway causes less postanaesthetic sore throat than endotracheal intubation.[11,12]

Maintenance of anaesthesia

Following the induction stage, the maintenance of anaesthesia throughout surgery will require the use of either an intravenous agent or a volatile anaesthetic agent added to the inspired gases. Commonly used maintenance agents are intravenous propofol, given as a continuous infusion from a syringe pump, and inhalational isoflurane, with or without the concomitant use of inhaled nitrous oxide (N_2O). Other commonly used volatile anaesthetic agents include sevoflurane and halothane. Halothane is now rarely used in adult practice, but it has remained the mainstay of anaesthesia for infants and children because of its lack of pungency. Sevoflurane has the potential to supersede halothane because of its lack of airway irritability, more rapid recovery and improved safety profile.[13]

Choosing the optimal anaesthetic regimen

Examination of the literature and discussion with anaesthetists showed that there is much variation in the agents (and doses of agents) used in everyday practice. Decisions that anaesthetists make about the best regimen to use will reflect issues of clinical effectiveness, safety, patient acceptability, cost and their familiarity with the technique.

Clinical effectiveness

Although long-term clinical outcome after day surgery has not been shown to be affected by anaesthetic technique, several studies appear to show that the choice of technique has an impact on the short-term outcome. Indicators of short-term outcome have included: the time to eye opening, the time to standing unaided, the time

to being ready for discharge from the recovery room to the ward, the pain levels experienced in hospital, the rates of postoperative nausea and vomiting (PONV), indicators of fatigue and the time to reach the criteria for discharge home.[14]

Longer term clinical indicators that have been used to assess the effectiveness of anaesthesia include: the rate of unplanned postoperative admission, the rate of readmission, contact with a general practitioner (GP) in the first 24 hours after discharge, contact with the hospital in the first 24 hours after discharge, pain after discharge, PONV after discharge and the time to return to normal activity.

PONV is the most commonly investigated side-effect in day-case anaesthesia and surgery, with a reported average incidence of 36% in the UK.[15] Factors that influence PONV include the type of surgery, the duration of surgery, the gender of patient, the age group of patient and the use of certain drugs (N_2O, opioids, anti-emetics, premeditation). However, published reports show a wide range of PONV rates, even for the same procedure (e.g. studies of gynaecological laparoscopy patients show a range of 0–96%).[16] Guidelines have been published that recommended the reduction of PONV to 10%.[17] PONV is an important cause of unscheduled hospital stays in day surgery. Meaden and co-workers[18] from Norfolk and Norwich Hospital reported that 3.6% of day-surgery patients were admitted overnight in 1992 and 2.7% in 1993. Of these, 42.6% and 20.9% of admissions, respectively, were due to PONV.

Patient acceptability

Patients who undergo day surgery are generally healthy and in hospital for a minimum period of time. Issues concerning their care can be expected to be different from those for other patient groups. Common side-effects after day surgery are PONV, pain, drowsiness and fatigue. These side-effects are generally transitory and do not persist beyond 4 days after surgery. A British survey of adult day-surgery patients showed that pain worsens following discharge, increasing on the journey home and persisting for several days. It took up to 72 hours for mean pain scores to decrease to the levels reported at discharge. The incidence of nausea increased three-fold during the journey home and took 48 hours to return to discharge levels. Most patients (70%) felt that pain was a problem and 44% felt that nausea was a problem.[19] Admissions to hospital are usually for medical or surgical reasons, such as pain. Anaesthetic-related admissions may be due to PONV, somnolence or aspiration.[20] Preliminary studies have shown that patients place value on avoiding these transitory but unpleasant sequelae. Hawksworth[21] reported that patients were willing to pay for the improved outcomes associated with propofol and ondansetron, as compared to thiopentone or metoclopramide.

Economic evidence

The cost of anaesthesia has historically been combined with the costs of surgery. Indeed, there are some sources of cost that can be difficult to attribute solely to anaesthesia or solely to surgery. However, there are increasingly robust anaesthesia costing methods available.[22,23] The use of patient-based (bottom-up) costs, rather than average (top-down) costs or charges is required if differences between anaesthetic techniques are to be identified.

Anaesthesia-costing studies show that the cost of drugs is a small proportion of the total anaesthetic cost, being as low at 4% in day surgery[23] and sometimes less than 1% in inpatient surgery.[22] Organisational and operational factors within institutions are likely to have a much more significant effect on costs. A 30-minute delay in the start of an operating session can be equivalent to the cost of 2 hours of anaesthesia using a propofol infusion.[23]

Anaesthetic agents vary widely in terms of acquisition and administration costs. At induction, for example, propofol can cost £4 per patient, compared with £1 per patient for thiopentone. During maintenance anaesthesia, the hourly cost for an adult is around £12 for propofol, £1.50 for halothane, £6 for enflurane, £12 for isoflurane and £12 for sevoflurane.[22,24]

There were 2.2 million reported day-case admissions for surgical procedures in England for the year 1994–95.[23] Although drug costs are dwarfed by other costs, the aggregated cost of drugs is considerable. If all these operations had used the cheapest possible agents, the annual cost would have been £2.2 million. A policy switch to use the most expensive option available would have cost around £26.4 million.

The newer anaesthetic agents are perceived to be the more costly. However, since the costs (usually unmeasured) of healthcare resources, the time to recovery and side-effects also differ, the higher price of the more expensive agents may be offset by reductions in recovery and discharge time, and

a reduced incidence of side-effects, such as PONV. It is also possible that, in the longer term, using intravenous agents may reduce equipment costs (vaporisers and gas-scavenging systems).

Cost differences between inhalational agents are due to differences in drug-acquisition costs and differences in potency. Other relevant issues in costing inhalational agents are the use (or not) of N_2O, although this only costs £0.60 per hour,[25] and the use of low-flow anaesthesia, in which much smaller quantities of inhalational agent are vaporised because the anaesthetic gases are recirculated in the breathing system. Both techniques significantly reduce the consumption of anaesthetics and must be standardised within a study design.[26,27] To assess whether there is a true difference in resource use, other than acquisition costs, between different agents it is necessary to obtain accurate information on resource use for the anaesthetic and postanaesthetic periods. Costing the anaesthetic period is complicated, since most operating theatre management systems have no information about the cost of providing general anaesthesia.

Economic evaluations of anaesthetic drugs in the context of day surgery are now more common, but vary in quality and design. Three recent studies on anaesthetic techniques for day-case arthroscopy of the knee,[28–30] using 'time to home readiness' as the outcome measure, found no differences between the techniques studied, but there were marked differences in the methods used. Two of the studies reported PONV rates, one finding no PONV[28] and one finding rates in excess of 40%,[29] suggesting that there were large differences in the practice, definition or scale of measurement used. All three studies reported a reduction in costs for the inhalational techniques over the intravenous (principally propofol) techniques, and thus recommended the inhalational option. Costs reported were divided into variable costs and staff costs,[30] drug costs and nursing costs[29] and drug costs only.[28] Different types of intravenous or inhalational anaesthetic agents were evaluated in each of the three studies. These differences in approach limit the comparability between the studies in terms of costs or outcomes, and thus limit their use to inform decision-making.

Current day-surgery anaesthetic practice

Despite a recent study[31] suggesting that anaesthetic practice reflects published evidence in over 80% of procedures, published evidence does not always give clear information to anaesthetists to aid in the selection of anaesthetic agents and the preparation of an anaesthesia plan. For a variety of reasons, there appears to be wide variation in anaesthetic practice. The most recent and the largest UK postal survey of day-surgery anaesthetic practice was carried out by Simpson and Russell,[32] who focused on anaesthetic practice for day-case gynaecological laparoscopy in the UK. The response rate from 243 hospitals in the study was 72%. It was found that in this kind of day surgery few anaesthetists (19%) now regularly use premedication, and induction is almost invariably with propofol. For maintenance of anaesthesia, most (59%) use isoflurane, 20% use enflurane, 11% use sevoflurane, 9% use propofol, 5% use desflurane and 3% use halothane. Most anaesthetists use N_2O.

The study also found that a wide range of analgesic drugs are used. Most use alfentanil or fentanyl intraoperatively, but 21% use morphine, diamorphine or pethidine. In addition, nearly all (94%) use non-steroidal anti-inflammatory drugs (NSAIDs). Half (50%) use some form of local anaesthetic technique. In this subgroup, most give bupivacaine into the wound (43%) or intraperitoneally (20%).

Around half (52%) of respondents believed that a continuous infusion of propofol reduces PONV, but had strongly held reasons for not using it: ease of use of volatile agents (61%); perceived lack of clinical benefit (28%); cost (18%); unfamiliarity (11%); and lack of suitable equipment (10%). Prophylactic anti-emetics were "always used" by the majority (61%), and in this subgroup intravenous ondansetron 4 mg was the commonest choice (59%). When confronted with PONV, nearly all (91%) prescribed anti-emetics, the commonest drugs used being ondansetron (44%) and prochlorperazine (43%).

The survey by Simpson and Russell[32] illustrated the variation in anaesthetic practice in gynaecology, and it is probable that a similar variation occurs in other adult and paediatric anaesthetic practice.

In the present study, it was considered essential to obtain better information on current patterns of anaesthesia practice, for two main reasons. First, it was necessary to identify the principal models of paediatric practice that would be evaluated in the empirical study, and to this end a pre-pilot survey was carried out. Second, it appeared important to identify the amount of variation in current practice in order to understand the limits to the extra-

polation and applicability of the results obtained. A national postal survey of anaesthetists was therefore carried out. Issues covered included: the induction and maintenance agents used for adults and children in different procedures, and the use of anti-emetics, local anaesthetics, intraoperative pain relief, N_2O and low-flow anaesthesia.

The rationale for an economic evaluation of anaesthesia in day surgery

In common with other areas of healthcare provision, anaesthesia is subject to cost-containment pressures. Drug costs are easily identifiable targets for savings, and therefore anaesthetists are likely to feel the pressure of cost-cutting initiatives. More economic evaluations of anaesthetic techniques and drugs are published every year, and the anaesthetist is increasingly called upon to incorporate this information in their practice. Economic evaluations determine the incremental difference in cost and outcome between two interventions. This provides decision-makers with information on the clinical and financial implications of choosing one of the alternatives.

Patient outcomes in economic evaluations can be measured in three different ways:

- Clinical effectiveness, measured by natural units (e.g. rates of PONV), is used in cost-effectiveness analysis. When the effectiveness of two alternatives is shown to be equivalent, the evaluation becomes a cost-minimisation analysis.
- Utility (a subjective measure of the value of a health state) is used in cost–utility analysis. Quality-adjusted life-years (QALYs) are the usual unit of measurement.
- Cost–benefit analysis uses monetary valuations (e.g. willingness to pay) to quantify outcome.

Cost-effectiveness analysis

Clinical indicators, such as time to eye opening and orientation in the recovery room, have been used extensively in the assessment of anaesthetic drugs. However, statistically significant differences between these early postoperative indicators do not necessarily translate into clinically significant differences that persist beyond the first few post-operative hours. In these situations, they have little role in evaluating the impact of anaesthetic techniques. Longer term clinical indicators, such as postdischarge PONV, unanticipated readmissions and time taken to return to work, are considered to be of more use. In the CESA project, clinical outcomes were used to assess real clinical differences, if short term, between principal models of anaesthesia in the adult and paediatric populations. The size of the empirical study was determined using PONV as the primary clinical endpoint because this is the principal useful clinical endpoint used in comparing day-surgery anaesthetic techniques. The use of PONV determined that a cost-effectiveness analysis would be carried out. Differences in PONV rates gave incremental costs per episode of PONV avoided.

Cost–benefit analysis

Cost–utility analysis and cost–benefit analysis encompass valuations of the whole impact of the intervention on the patient, not captured by cost-effectiveness analysis, such as the (dis)comfort of induction, pain, drowsiness or fatigue, which are important attributes of patient acceptability. Currently, patients' perceptions and preferences for anaesthesia do not necessarily drive treatment choices. However, there is now emerging evidence that patients have strong preferences and attitudes about the anaesthetic process.[33] Therefore, in this study, consideration was given to the multi-attribute nature of the patient's utility function; that is, their valuation of their outcomes from the process of anaesthesia. However, valuations of the process of anaesthesia and postoperative recovery from anaesthesia were required, rather than valuations of postoperative survival or long-term health status. This would suggest that measures of health status or health-related quality of life, weighted for survival (e.g. QALYs), would not be appropriate for these populations. Two suitable methods for the measurement of processes of care are conjoint analysis and contingent valuation (CV). Both techniques come under the heading of 'stated preference' (compared with revealed preference). This umbrella term refers to techniques that attempt to establish individuals' preferences by presenting them with hypothetical scenarios.

The CV method is used to elicit values for items not typically traded in private markets, such as health. Respondents are asked to attach hypothetical monetary values to goods, services or health changes. Valuation is based on the contingency that a hypothetical market for health does in fact exist. The CV method accounts for both health and non-health effects and is thus considered to be a comprehensive measure of the effects of a healthcare technology.[34] The importance of non-health effects to patients is illustrated clearly in a study examining patients'

willingness to pay for autologous blood donation.[35] The willingness to pay of respondents informed about actual risks far outweighed the cost of the service. The interventions studied in this report offer virtually no health benefits, but evidently offer substantial intangible benefits in the form of 'peace of mind'. The CV method is increasingly being applied to elicit preferences regarding the use of pharmaceuticals (e.g. in hypertension, lipid-lowering and depression).[36–38] The CV method has also been used to elicit preferences for side-effect avoidance. O'Brien and co-workers[38] elicited willingness-to-pay values for the seven principal side-effects of antidepressants, and identified those "most troublesome" to patients.

The CV method was therefore considered an appropriate method to elicit preferences in day-surgery anaesthesia. Prior to this study, a CV method tool was developed and tested to identify and quantify women's preferences for alternative anaesthetic agents in day surgery.[33] In this study, this tool provided 'net benefit' valuations (see page 44) from a randomised sample to be incorporated in a cost–benefit analysis.

The rationale for a randomised controlled trial design

This study examined the clinical, patient preference and cost differences between the main day-surgery general anaesthesia models of practice in the UK, using a pragmatic randomised controlled trial (RCT) design. RCTs are regarded as the gold-standard design in scientific medical research because the effects of bias are minimised through accepted methodological and design features. However, generalisability to normal practice can be reduced if the protocol is too rigid and does not reflect normal practice patterns. The treatment protocol for this trial reflected routine practice to ensure that the results are applicable to NHS practice.

The alternative methods of anaesthesia under investigation and the treatment protocol were selected on the basis of the literature review and the pilot phase of the paediatric national survey, as well as ratification by a scientific advisory group convened specifically for this study.

Aims and objectives of the study

The aim of this study was to assess the relative cost-effectiveness of alternative anaesthetic agents in adult and paediatric day surgery using a naturalistic RCT design.

The principal objectives relating to the principal anaesthetic methods used in adult and paediatric day surgery, were:

- to assess the relative clinical outcomes
- to identify resource use and the associated costs incurred by the NHS during the anaesthetic and postanaesthetic periods
- to determine the acceptability to patients of the principal anaesthetic methods used
- to use the clinical, economic and patient-based outcomes data collected in this study to assess the relative cost-effectiveness of the different anaesthetic regimens.

Furthermore, the methods used and the size of the study ensured that the results are credible, relevant and accessible to anaesthetists and surgeons, and to healthcare decision-makers at both local and national level. An evaluation of the safety of the different anaesthetic techniques was not part of this study.

Chapter 2

Literature review

Aims and objectives of the review

The aim of the literature review was to provide a comprehensive and critical analysis of the currently available evidence to place the study in context, facilitate the use of accepted research methods and provide additional secondary data for the economic analysis.

The objectives of the review were to:

- Inform the project of the following aspects of anaesthesia in adult and paediatric day surgery:
  - current practice patterns, variations and trends
  - relative effectiveness, costs, cost-effectiveness and patient-based outcomes.
- Inform the practice survey.
- Produce a literature review that provides quality-assessed clinical, economic and patient-based outcomes data and information on practice variation for the economic analysis, using standard quality-assessment indicators.
- Produce a literature report that provides a comprehensive and critical analysis of the evidence currently available.

The section below details the search strategy and quality criteria used, and the following three sections provide a summary of the current evidence of the relative effectiveness, the impact on patient-based outcomes and the costs of the principal anaesthetic agents and techniques used in day-surgery general anaesthesia. Standard quality-assessment indicators are used to indicate the quality of the literature in each area. The last section gives a summary of the current level of evidence.

Search strategy

Although not a formal systematic review, the search strategy used in this study follows the NHS Centre for Reviews and Dissemination Guidelines[39] in order to minimise biases and random errors. The principal components of the search strategy were:

- sources of evidence (databases searched and keywords used)
- an assessment of the quality of the evidence
- the inclusion and exclusion criteria for the studies (see appendix 1).

Sources of evidence

The range of databases interrogated cover relevant medical, pharmaceutical, economic, sociological, organisational and methodological evidence (to December 2000) (see appendix 1).

In addition to the review of primary studies, good-quality systematic reviews and meta-analyses were included if there was evidence of a literature search strategy, explicit inclusion criteria, a valid assessment of primary studies and an appropriate pooling or summary. Relevant systematic reviews were identified from the NHS Centre for Reviews and Dissemination database, which reports the results of reviews from 1994 onwards. Systematic reviews before this period were identified from MEDLINE and EMBASE using a recommended search strategy.[39]

Nine meta-analyses were located (see appendix 2).[40–48] These compared the rates of PONV with different anaesthetic methods. However, eight included inpatient surgery studies, and so may be of limited direct relevance to the present study. One systematic review on postoperative analgesia and PONV in day surgery was obtained[44] (discussed on page 15). No systematic reviews were found that specifically or sufficiently addressed the impact of different anaesthetic agents on adult or paediatric patients in day surgery.

Quality assessment of the literature found

In this study, the quality assessment of literature had two objectives:

- to generate a statement on the quality of evidence available in each area reviewed
- to assess the literature for economic analysis modelling.

Quality assessment was undertaken of all clinical, patient-based outcomes and economic studies

included in the following sections. A standard method of data extraction and assessment was used (available from the authors on request). The studies were categorised using accepted hierarchies of evidence from the NHS Centre for Reviews and Dissemination report published in 1996[39] (see appendix 3).

RCTs and observational studies were assessed using a published checklist[39] (see appendix 3).

Patient-based outcome studies were assessed on two levels. First, the study design was assessed using the checklists for RCTs and observational studies. Second, an attempt was made to assess the quality of the instruments used in the study. Criteria are less well developed for this aspect of studies, and it was not feasible to subject each instrument to a formal quality assessment. The checklist proposed by Fitzpatrick and co-workers[49] was used to assess the quality of these studies (see appendix 3).

The quality of costing and economic studies was assessed (see appendix 3) using the *British Medical Journal* 35-point checklist.[50] All the papers retrieved for the economics literature review were screened for inclusion using the following criteria:

- An evaluation was included of anaesthetic techniques, procedures or agents in the context of day surgery.
- Papers that reported evaluations of anaesthetic techniques, procedures or agents for inpatient surgery were excluded. This was to ensure that any comparisons made of extracted cost or patient outcome data were generalisable to the setting of day surgery and not influenced by factors specific to inpatient surgery (e.g. organisation of pre-, peri- and postoperative care, use of different or additional drugs and procedures that may affect the outcomes and resource use associated with general anaesthesia).
- The evaluation included cost and outcome data for comparison of specific anaesthetic techniques, procedures or agents for general anaesthesia. Sufficient data were reported to extract costs and outcome data relevant to comparisons of anaesthetic techniques, procedures and agents for the literature review or the economic model.
- The evaluations were based on primary data collection or systematic review.

Studies included in the review

The following studies were included in the final review:

- 89 adult clinical outcome studies[29,30,51–137]
- 30 paediatric clinical outcome studies[13,138–166]
- 9 meta-analyses[40–48]
- 39 adult patient-based outcome studies[19,21,33,77,79,89,108,167–198]
- 13 paediatric patient-based outcome studies[147,199–210]
- 24 costing and economic studies.[22,28,29,84,86,99,125,126,129,175,211–224]

Tables summarising these studies are given in appendices 4 to 9. A list of excluded studies is given in appendix 10.

Clinical reviews

Many studies have examined different techniques of anaesthesia for day or short-stay procedures. Unfortunately, the number of different variables examined has also been considerable, including onset of anaesthesia, quality of surgical conditions, cardiovascular effects and respiratory effects. Postoperatively, many different techniques have been used to assess recovery and evaluate side-effects. Unfortunately, the number of drugs available also means that most studies cannot be compared directly because they use different combinations of drugs, or because they use the same drugs but given in different ways (e.g. fixed dose, dose according to body weight). Recovery has been measured in a variety of different ways, with some studies using simple tests, such as time to eye opening, and some using complex computer-driven psychometric tests, making direct comparison difficult.

The quality of the studies reported varies considerably. There are few truly convincing RCTs. Most were randomised, or pseudo-randomised. Few studies were fully blinded. Commonly, blinded recovery assessments were carried out, but the group allocation was otherwise open.

For the purposes of this review, the measurement of clinical outcomes has been grouped into five areas of recovery assessment,

- Early recovery
  - time to eye opening
  - time to protrude tongue on command
  - time to awaken.
- Intermediate recovery
  - time to give the correct date of birth, location, day and date
  - time to full orientation when the patient is fit to move from first to second stage recovery.

- Late recovery
  - time to walk unaided
  - ability to walk in a straight line
  - time to discharge home.
- Psychomotor recovery
  - digital symbol substitution test
  - P-deletion test (and its variants)
  - dot tracking on a computer screen
  - Trieger dot test
  - critical flicker fusion threshold
  - mood adjective checklist
  - perceptual accuracy tests
  - picture cards recall
  - word association or recall
  - perceptual memory
  - pegboard test
  - simple reaction time
  - choice reaction time
  - body sway coordination tests
  - finger tapping
  - Maddox Wing
  - Aldrete score (postanaesthesia recovery score looking at activity, respiration, circulation, consciousness and colour).
- Unwanted side-effects
  - PONV
  - pain (visual analogue scale (VAS) scores)
  - anxiety (VAS scores).

Adult clinical review

This section examines research on the impact of anaesthesia techniques in day surgery on adult clinical outcomes.

Summary of clinical evidence

Eighty-nine comparative studies of anaesthesia in adult day surgery were included in the review (see appendix 4 for a summary of each study). The anaesthetics compared in these studies are summarised in *Table 1* (the sum is more than 89 because more than one comparison was carried out in some studies).

Evidence for clinical differences

The 89 studies were graded for quality of evidence, 84 were grade I, four were grade II-1a and one was grade II-1b. Most studies were small RCTs, with patient groups smaller than 50 in 36 of the studies. The studies came primarily from the USA or Canada (30), the UK (23), Sweden (7), Finland (9) and Denmark (5). The outcome measures most commonly used were times to different stages of emergence and recovery and PONV. Forty-five studies did not report the time to, or readiness for, discharge from hospital. Fifty-seven studies reported PONV rates in hospital. Only four studies reported Aldrete scores. A range of pain scores and use of analgesics were reported.

Induction of anaesthesia

The equivalence of doses for induction of anaesthesia is difficult to address. Few of the studies compared two induction agents with all else remaining constant. The interpretation of the studies must, therefore, allow for this matter. The intravenous agents may also not have been given in equipotent doses, and in some cases a fixed dose was given without regard to body weight or habitus. The accurate direct comparison of intravenous and inhalational agents is actually impossible. These agents are given in different ways, and thus onset pharmacokinetics cannot be compared. Inhalational agents can be compared directly with one another by using the concept of minimum alveolar concentration (MAC). Intravenous agents can be compared directly for induction and also for maintenance (minimum infusion rate (MIR)). It is not possible to compare the MAC with the MIR because they are only equipotent at one point: 1.0 × MAC = 1.0 × MIR, by definition. The log dose–response lines may not, however, be parallel and so 2.0 × MAC is unlikely to be equipotent to 2.0 × MIR. Furthermore, the relationship between the MAC for anaesthesia and the MAC at which the patient recovers consciousness (MAC awake) varies between volatile anaesthetic agents.

Propofol and thiopentone

Of the 16 studies[61,65,66,77,85,87,88,91,102,111,118–121,136] that compared the two induction agents thiopentone and propofol, in only six was the remainder of the process of anaesthesia kept constant in the two groups. Whether considering only these six studies or taking all 16 together, however, the conclusion remains the same. In no case was thiopentone better than propofol. Five studies found no difference between the two agents, but in all other studies propofol was superior to thiopentone with respect to early, intermediate, late and psychomotor recoveries.

Propofol and etomidate

Two studies compared these two induction agents.[65,97] The first study is not a well-performed study. Propofol was administered not as a bolus, but using a target controlled system in the first group. Etomidate was administered as a bolus of 0.25 mg/kg in the second group, and anaesthesia continued in that group using isoflurane. Early recovery was more rapid in the etomidate group, but there was otherwise no difference between the groups. In the second study, propofol was

TABLE 1 *Comparisons under study in the review of anaesthesia in adult day surgery*

Comparison	No. of studies	Studies
Propofol vs thiopentone induction	16	Chittleborough *et al*., 1999;[61] De Grood *et al*., 1987;[65] Ding *et al*., 1993;[66] Gupta *et al*., 1992;[77] Kashtan *et al*., 1990;[85] Korttila *et al*., 1990,[88] 1992;[87] Lim and Low, 1992;[91] Nielsen *et al*., 1991;[102] Price *et al*., 1998;[111] Ryom *et al*., 1992;[118] Sampson *et al*., 1988;[119] Sanders *et al*., 1991;[120] Seegatto *et al*., 1993;[121] Wetchler *et al*., 1992[136]
Propofol vs etomidate induction	2	De Grood *et al*.,1987;[65] Moffat and Cullen, 1995[97]
Propofol vs methohexitone induction	3	Cade *et al*., 1991;[56] Werner and Newhouse, 1993;[135] Sun *et al*., 1999[222]
Isoflurane vs sevoflurane induction	1	Sloan *et al*., 1996[124]
Propofol vs sevoflurane induction	5	Dashfield *et al*., 1998;[64] Fish *et al*., 1999;[72] Fredman *et al*., 1995;[74] Ong *et al*., 2000;[106] Smith and Thwaites, 1999[125]
Thiopentone vs sevoflurane induction	1	Patil *et al*., 1999[107]
Propofol vs desflurane induction	5	Apfelbaum *et al*., 1996;[51] Lebenbom-Mansour *et al*., 1993;[90] Rapp *et al*., 1992;[116] van Hemeirjick *et al*., 1991;[133] Wrigley *et al*., 1991[137]
Thiopentone vs desflurane induction	1	Fletcher *et al*., 1991[73]
Sevoflurane vs desflurane maintenance	3	Naidu-Sjosvard *et al*., 1998;[98] Nathanson *et al*., 1995;[100] Tarazi and Philip, 1998[130]
Isoflurane vs desflurane maintenance	3	Gupta *et al*., 1996;[79] Martikainen *et al*., 2000;[95] Wagner and O'Hara, 1995[223]
Sevoflurane vs isoflurane maintenance	4	Eriksson *et al*., 1995;[68] O'Hara *et al*., 1996;[104] Philip *et al*., 1996;[108] Sloan *et al*., 1996[124]
Propofol vs isoflurane maintenance	19	Ashworth and Smith, 1998;[53] Chung *et al*., 2000;[62] Collins *et al*., 1996;[63] Green and Jonsson, 1993;[75] Gupta *et al*., 1995;[78] Killian *et al*., 1992;[86] Korttila *et al*., 1990;[88] Larsen *et al*., 1992;[89] Lim and Low, 1992;[91] Marshall *et al*., 1992;[93] Martikainen *et al*., 2000;[95] Moffat and Cullen, 1995;[97] Nelskyla *et al*., 1999;[101] Nightingale and Lewis, 1992;[103] Oikkonen, 1994;[105] Pollard *et al*., 1994;[109] Valanne, 1992;[132] Werner and Newhouse, 1993;[135] Wetchler *et al*., 1992[136]
Halothane vs isoflurane maintenance	2	Carter *et al*., 1885;[58] Pollard *et al*., 1994[109]
Enflurane vs halothane maintenance	3	Biswas and Hatch, 1989;[55] Carter *et al*., 1885;[58] Pollard *et al*., 1994[109]
Isoflurane with or without nitrous oxide	3	Hovorka *et al*., 1989;[82] Melnick and Johnson, 1987;[96] Short *et al*., 1985[122]
Desflurane with or without nitrous oxide	3	Fletcher *et al*., 1991;[73] Rapp *et al*., 1992;[116] Wrigley *et al*., 1991[137]
TIVA with or without nitrous oxide	4	Arellano *et al*., 2000;[52] Lindekaer *et al*., 1995;[92] Sukhani *et al*., 1994;[127] Tang *et al*., 1999[129]

continued

***TABLE 1* contd** *Comparisons under study in the review of anaesthesia in adult day surgery*

Comparison	No. of studies	Studies
Propofol vs sevoflurane maintenance	8	Carroll *et al.*, 1997;[57] Fish *et al.*, 1999;[72] Fredman *et al.*, 1995;[74] Nelskyla *et al.*, 1999;[101] Ong *et al.*, 2000;[106] Raeder *et al.*, 1997;[112] Smith and Thwaites, 1999;[125] Song *et al.*, 1998[126]
Enflurane vs isoflurane maintenance	3	Chung *et al.*, 2000;[62] Hovorka *et al.*, 1989;[82] Pollard *et al.*, 1994[109]
Propofol vs desflurane maintenance	10	Apfelbaum *et al.*, 1996;[51] Ashworth and Smith, 1998;[53] Carroll *et al.*, 1997;[57] Eriksson and Korttila, 1996;[69] Lebenbom-Mansour *et al.*, 1993;[90] Martikainen *et al.*, 2000;[95] Raeder *et al.*, 1998;[113] Rapp *et al.*, 1992;[116] Tarazi and Philip, 1998;[130] van Hemeirjick *et al.*, 1991[133]
Propofol vs enflurane maintenance	3	Chung *et al.*, 2000;[62] Ding *et al.*, 1993;[66] Pollard *et al.*, 1994[109]
Propofol vs halothane maintenance	2	Pollard *et al.*, 1994[109,224]
Alfentanil vs halothane or enflurane	1	Biswas and Hatch, 1989[55]
Alfentanil vs fentanyl or enflurane	1	Haley *et al.*, 1988[80]
Alfentanil vs remifentanil	1	Cartwright *et al.*, 1997[59]
Alfentanil vs isoflurane	1	Short *et al.*, 1985[122]
Fentanyl vs ketamine	1	Fabbri *et al.*, 1995[70]
Propofol vs thiamylal–enflurane	1	Randel *et al.*, 1992[115]

compared with etomidate, both given by a total intravenous technique. Early and intermediate recovery was faster in the propofol group, but psychomotor recovery was the same with both agents.

Propofol and methohexitone

Three studies compared propofol with methohexitone for induction.[56,135,222] The evidence supports propofol 2–2.5 mg/kg as being a superior induction agent over methohexitone 1.5 mg/kg. As methohexitone was withdrawn from clinical practice in the UK in 1999, the importance of these studies has reduced significantly.

Inhalational agents

Only one study compared two different inhalational agents for induction of anaesthesia.[124] Following a midazolam premedication, a single vital capacity breath of either 5% isoflurane or 5% sevoflurane was given. Maintenance of anaesthesia was continued using the same inhalational agent. No differences were found with respect to early, intermediate, late or psychomotor recoveries.

Intravenous induction compared to inhalational induction

Propofol and sevoflurane

Five studies comparing these two agents were found.[64,72,74,106,125] Fredman and co-workers[74] examined two groups of patients, one of which received propofol 1.5–2.0 mg/kg for induction of anaesthesia, and the other sevoflurane 3–4%. In both groups maintenance of anaesthesia was identical (sevoflurane and N_2O). There was no difference between the groups with respect to early, intermediate or late recovery. Dashfield and co-workers[64] studied 40 patients, half of whom received induction of anaesthesia with propofol given to loss of consciousness (mean dose 3.2 (standard deviation (SD) 0.4) mg/kg) and half of whom took a single vital capacity breath of 8% sevoflurane. Anaesthesia was continued with sevoflurane and N_2O in all cases. There was no difference in early or psychomotor recovery between the two patient groups. Smith and Thwaites[125] compared a total intravenous technique using propofol with a total inhalational technique using sevoflurane. The sevoflurane group demonstrated a more rapid early,

intermediate and late recovery. Ong and co-workers[106] also compared propofol total intravenous anaesthesia (TIVA) with sevoflurane total inhalational anaesthesia. There was no difference with respect to early and intermediate recovery, but N_2O was given to one group (sevoflurane) only. Fish and co-workers[72] also found no difference with respect to early and intermediate recovery. In the final study, which examined propofol and sevoflurane induction of anaesthesia, no measurements of recovery were made.[125]

Thiopentone and sevoflurane
One study[107] compared these two agents for induction. Sevoflurane was superior to thiopentone in terms of the number of patients able to walk unaided after 30 minutes. There was a higher incidence of arrhythmias in the thiopentone group.

Thiopentone and desflurane
One study[73] compared these two agents for induction. Four separate patient groups were included, and in two groups the only difference was the induction agent, thiopentone 5 mg/kg or desflurane. Thiopentone was inferior to desflurane with respect to intermediate recovery and choice reaction time, but not with respect to critical flicker fusion threshold.

Propofol and desflurane
Five studies were found.[51,90,116,133,137] Apfelbaum and co-workers[51] studied 20 volunteers, each of whom received a different anaesthetic technique on four separate occasions. Two of these techniques differed only with respect to induction of anaesthesia (propofol 2.5 mg/kg or desflurane 3%), desflurane being used for maintenance. With respect to early and intermediate recovery, those who received desflurane for induction recovered more rapidly. Late recovery measurements showed no differences between the groups. The psychomotor tests at 1 hour showed a number of differences, but the first group was better at some tests and the second at others, and there was no difference in the remainder. Psychomotor tests beyond 1 hour showed no difference between the groups. A similar set of four anaesthetic techniques was examined in the remaining studies. There was no difference between the propofol induction and desflurane induction groups with respect to early, intermediate, late or psychomotor recoveries.

Maintenance of anaesthesia

Isoflurane and sevoflurane
Four studies compared these two agents for maintenance.[68,104,108,124] In two studies[68,108] propofol was used for induction and fentanyl for analgesia. In both studies, early, intermediate and psychomotor studies showed sevoflurane to be superior to isoflurane, although there was no difference with respect to late recovery. In a third study,[104] involving patients who received thiopentone for induction, there was no difference between isoflurane and sevoflurane. The fourth study[124] used the same agent (sevoflurane or isoflurane) for induction of anaesthesia by single vital capacity breath, and demonstrated no difference between sevoflurane and isoflurane.

Isoflurane and halothane
These two agents were compared in two studies.[58,109] All patients received propofol for induction of anaesthesia. No difference was found in the results of psychomotor tests between the patients who received isoflurane and those who received halothane.

Isoflurane and enflurane
Three studies[62,82,109] compared this pair of agents for maintenance of anaesthesia following propofol for induction. Pollard and co-workers[109] found that enflurane was better than isoflurane in terms of psychomotor recovery. Chung and co-workers[62] found no difference with respect to early, intermediate or late recovery. Hovorka and co-workers[82] found no difference in terms of PONV.

Enflurane and halothane
Three studies compared these agents for maintenance of anaesthesia.[55,58,109] Pollard and co-workers[109] used propofol for induction. Those patients who received enflurane recovered more rapidly than those who received halothane, although only psychomotor tests were used. Biswas and Hatch[55] used thiopentone for induction. Enflurane was better than halothane with respect to early and intermediate recovery, but no difference was found with respect to psychomotor recovery. Carter and co-workers[58] standardised induction and used propofol. No difference in recovery was found between enflurane and halothane.

Sevoflurane and desflurane
These two maintenance agents were compared in three studies.[98,100,130] All studies used propofol for induction of anaesthesia and also used an opioid (fentanyl in the first two, and alfentanil in the third). All patients in the first two studies received N_2O, whereas none did so in the third study. Two studies[98,100] showed early recovery from desflurane to be faster than sevoflurane, but in the third study there was no difference. There was no difference

with respect to late recovery in any study. Psychomotor recovery after desflurane was faster than after sevoflurane in the absence of N_2O, but in those patients who received N_2O there was no difference.

Isoflurane and desflurane
These agents were compared in three studies,[79,95,223] all of which used propofol for induction. Gupta and co-workers[79] and Rieker[226] added either fentanyl or alfentanil. A fourth study[73] used thiopentone for induction, with no opioid. In all cases desflurane was better than isoflurane with respect to early and intermediate recovery, but there was no difference between the agents with respect to later recovery. In the patients who had received propofol for induction, psychomotor recovery was better after desflurane than after isoflurane, although there was no difference between the two agents when thiopentone was used for induction.

Propofol and sevoflurane
Seven studies compared sevoflurane with propofol for maintenance anaesthesia.[57,72,74,106,113,125,126] Sevoflurane appears to be superior to propofol in its recovery characteristics (*Table 2*).

Propofol and desflurane
Ten studies compared these two agents for maintenance anaesthesia.[51,53,57,69,90,95,113,116,130,133] In all cases propofol was used for induction of anaesthesia. In most cases there were no differences. Desflurane was superior to propofol for early and intermediate recovery in three of the ten studies, and with respect to psychomotor recovery in one study. Propofol was better than desflurane with respect to late recovery in two studies. It would seem that any difference between these two techniques is of a minor and inconsequential nature.

Propofol and enflurane
These agents were compared in three studies.[62,66,109] Patients received propofol for induction of anaesthesia in two of the studies and thiamylal for induction in the third study. In two studies no differences were found between those patients who received enflurane and those who received propofol with respect to early, intermediate, late or psychomotor recovery. Both immediate and intermediate recovery were more rapid after propofol anaesthesia than after thiamylal–enflurane anaesthesia.

Propofol and halothane
These agents were compared in two studies.[109,224] All patients received propofol for induction of anaesthesia. In the first study, psychomotor recovery only was measured and this was found to be faster in those patients who received propofol than in those who received halothane. The second study found no difference with respect to intermediate, late or psychomotor recovery.

Propofol and isoflurane
Nineteen studies compared these two agents for maintenance anaesthesia.[53,62,63,75,78,88,91,93,95,97,86,89,101,103,105,109,132,135,136] Of those, 14 studies used propofol for induction followed by either propofol or isoflurane for maintenance. The remainder used thiopentone (three studies), methohexitone (one study) or etomidate (one study) for induction. The results are summarised in *Table 3*.

The studies in which propofol was used for induction support there being no differences between the propofol group or the isoflurane group with respect to early, intermediate, late or psychomotor recovery (see *Table 3*). In the other five studies, all patients in the propofol induction and maintenance group showed superior recovery characteristics for early, intermediate and later

TABLE 2 *Comparison of recovery after sevoflurane or propofol maintenance anaesthesia*

Study	Early recovery	Intermediate recovery	Late recovery	Psychomotor recovery
Carroll *et al.*, 1997[57]	S	S	S	S
Fish *et al.*, 1999[72]	ND	ND	NE	NE
Fredman *et al.*, 1995[74]	ND	ND	NE	NE
Ong *et al.*, 2000[106]	S	ND	P	NE
Raeder *et al.*, 1998[113]	S	S	ND	S
Smith and Thwaites, 1999[125]	S	S	ND	NE
Soing *et al.*, 1998[126]	ND	ND	ND	NE

ND, no difference; NE, not examined; P, propofol better than sevoflurane; S, sevoflurane better than propofol

TABLE 3 *Comparison of isoflurane and propofol for maintenance anaesthesia*

Study	Early recovery	Intermediate recovery	Late recovery	Psychomotor recovery	Induction agent
Ashworth and Smith, 1998[53]	ND	ND	ND	–	PR
Chung *et al.*, 2000[62]	ND	ND	ND	–	PR
Collins *et al.*, 1996[63]	ND	ND	ND	P	PR
Green and Jonsson, 1993[75]	I	ND	P	P	PR
Gupta *et al.*, 1995[78]	ND	ND	ND	I	PR
Killian *et al.*, 1992[86]	ND	P	P	ND	ET
Korttila *et al.*, 1990[88]	P	P	P	–	TH
Larsen *et al.*, 1992[89]	ND	ND	ND	ND	PR
Lim and Low, 1992[91]	P	P	P	–	TH
Marshall *et al.*, 1992[93]	ND	ND	ND	ND	PR
Martikainen *et al.*, 2000[95]	ND	ND	ND	–	PR
Moffat and Cullen, 1995[97]	P	P	P	–	ET
Nelskyla *et al.*, 1999[101]	I	I	ND	ND	PR
Nightingale and Lewis, 1992[103]	P	P	ND	ND	PR
Oikkonen, 1994[105]	P	P	–	ND	PR
Pollard *et al.*, 1994[109]	ND	ND	ND	P	PR
Valanne, 1992[132]	P	P	P	P	PR
Werner and Newhouse, 1993[135]	P	P	P	ND	MH
Wetchler *et al.*, 1992[136]	P	P	ND	–	PR

–, not stated; ET, etomidate induction in isoflurane group, propofol in TIVA group; I, isoflurane maintenance group superior; MH, methohexitone induction in isoflurane group, propofol in TIVA group; ND, no difference between groups; P, propofol maintenance group superior; PR, propofol for induction in all patients; TH, thiopentone induction in isoflurane group, propofol in TIVA group

recovery measurements to those in the other group. This suggests that TIVA using propofol is superior to a technique that uses any other induction agent followed by isoflurane. If the patients in the isoflurane group received propofol induction, however, such a difference was markedly reduced and almost eliminated. Using propofol as the induction agent would, therefore, seem to be the most important component of these comparisons.

Nitrous oxide

Most studies used N_2O as a part of the anaesthetic technique, although a few used oxygen-enriched air. There are ten studies where the only difference in technique between two groups is the giving of N_2O, with all other aspects being the same. In three of these studies desflurane was the maintenance agent[73,116,137] with desflurane used for induction in two. Thiopentone was used for induction in the third.[73] In all these three studies there were no differences between the N_2O and non-N_2O groups with respect to early, intermediate, late or psychomotor recoveries.

Two studies[55,96] used isoflurane with or without N_2O, and simply recorded "drowsiness" and PONV, respectively. They found no difference between the groups. One study[71] used enflurane with or without N_2O and recorded PONV. The difference in PONV was reported as significantly better without N_2O.

The other four studies[52,92,127,129] used a propofol TIVA technique and compared two groups, in only one of which N_2O was given. In two of these studies early recovery was measured and was shown to be faster in the group receiving no N_2O. No differences were found with respect to early recovery in the other two studies, or with respect to intermediate or late recovery in any study. In one study[127] the N_2O group was noted to have a lower propofol consumption due to a reduction in MAC, but propofol consumption was equal in the other studies.

Other techniques of maintenance of anaesthesia

Narcotic techniques of maintenance of anaesthesia have been studied in a small number of cases.

Alfentanil maintenance was compared with either halothane or enflurane,[55] and patients in the alfentanil group demonstrated a more rapid early recovery. Three groups in which alfentanil, fentanyl and enflurane were used for maintenance anaesthesia were examined in a second study.[80] Alfentanil was better than fentanyl, and both these agents were better than enflurane with respect to early, intermediate or late recovery. When remifentanil was compared to alfentanil[59] no difference was found with respect to early, intermediate or late recovery, although the patients in the remifentanil group performed better on psychomotor testing. Finally, fentanyl and low-dose ketamine were compared in one study.[70] Early recovery was better in the ketamine group, but no other differences were found.

Postoperative nausea and vomiting

Fifty-nine studies considered PONV. The variety of comparisons of induction and maintenance agents used makes it very difficult to draw firm conclusions. Forty-eight of the studies used propofol TIVA in one group. In only two studies was the rate of PONV lower in the comparator group than in the TIVA group, and in 21 studies the TIVA group showed a lower rate of PONV than the other group. It would appear that the least PONV is achieved using propofol administered by TIVA. Induction of anaesthesia using propofol was superior to induction of anaesthesia using a barbiturate or an inhalational agent. Patients who received induction of anaesthesia with desflurane were the most likely to suffer PONV. Finally, four studies examined the effects of N_2O on PONV. Three studies found there to be no difference between N_2O or oxygen-enriched air, and in one study the patients who received N_2O had more PONV.

A meta-analysis of PONV in day surgery compared propofol with other anaesthetics for induction and maintenance, although the results were presented only graphically.[44] This study appears to suggest that the use of propofol can reduce PONV rates in day surgery, although it was not possible to ascertain the actual reduction.

Paediatric clinical review

This section examines research on the impact of anaesthesia techniques in day surgery on clinical outcomes in paediatric patients.

Summary of clinical evidence

Thirty comparative studies of anaesthesia in paediatric day surgery were included in the review (see appendix 5 for details of each study). The anaesthetics compared in these studies are summarised in *Table 4* (the sum is more than 30 because more than one comparison was carried out in some studies).

Evidence for clinical differences

The 30 studies were graded for quality of evidence, and 27 were found to be grade I and three grade II-1a. Most studies were small RCTs, with patient groups smaller than 50 in 25 of the studies. The studies came from the USA or Canada (14), Finland (5), the UK (4), Japan (2), Australia (1), France (1), Sweden (1), Turkey (1) and Taiwan (1). The outcome measures most commonly used were times to different stages of emergence and recovery, and PONV. Seven studies did not report the time to, or readiness for, discharge from hospital. Only one study did not report the rate of PONV in hospital,[155] although only nine studies reported the rate of PONV after discharge. Only seven studies reported Aldrete scores (postanaesthesia recovery score looking at activity, respiration, circulation, consciousness and colour). A range of pain scores and the use of analgesics were reported.

Optimal induction

Most studies investigated induction in terms of the time spans involved. Parameters such as the time to loss of eyelash response and the time to intubation were used as measures of induction times. Nine studies[13,138,143,147,149,151,153,164,166] showed that sevoflurane provided a more rapid induction than halothane. Another study provided evidence that sevoflurane provided a more rapid induction than halothane, but the difference was not statistically significant. Kotiniemi and Ryhanen[148] reported that thiopentone provided a more rapid induction than halothane. The impact of different induction regimens on outcome measures is discussed below.

Thiopentone versus propofol

Six studies examined induction anaesthesia, three of which looked at propofol versus thiopentone.[139,146,157] Cheng and co-workers[139] reported a reduction in PONV in hospital with propofol, but Runcie and co-workers[157] and Hannallah and co-workers[146] did not find this. Runcie and co-workers[157] reported that early recovery was more rapid with propofol than with thiopentone, but earlier discharge occurred only in older children. However, the time from eye opening to discharge was 88 minutes for propofol compared with 117 minutes for thiopentone ($p = 0.004$). It is unlikely that these 29 minutes are clinically significant and can be translated

TABLE 4 *Comparisons under study in the paediatric review*

Comparison	No. of studies	Studies
Propofol vs thiopentone induction	3	Cheng *et al*., 1998;[139] Hannallah *et al*., 1994;[146] Runcie *et al*., 1993[157]
Propofol vs sevoflurane induction	2	Gurkan *et al*., 1999;[144] Viitanen *et al*., 1999[161]
Halothane vs thiopentone induction	1	Kotiniemi and Ryhanen, 1996[148]
Propofol vs halothane induction	4	Crawford *et al*., 1998;[140] Hannallah *et al*., 1994;[146] Ved *et al*., 1996;[160] Watcha *et al*., 1991[163]
Sevoflurane vs halothane induction + maintenance	11	Sury *et al*., 1996;[13] Ariffin *et al*., 1997;[138] Greenspun *et al*., 1995;[143] Johannesson *et al*., 1995;[147] Lermasn *et al*., 1996;[149] Meretoja *et al*., 1996;[151] Naito *et al*., 1991;[153] Piat *et al*., 1994;[155] Vitanen *et al*., 2000;[162] Walker *et al*., 1997;[164] Welborn *et al*., 1996[166]
Propofol vs isoflurane maintenance	3	Davis *et al*., 1997;[141] Hamunen *et al*., 1997;[145] Martin *et al*., 1993[150]
Halothane vs desflurane maintenance	2	Davis *et al*., 1994;[142] Welborn *et al*., 1996[166]
Propofol vs halothane maintenance	4	Moore and Underwood, 1994;[152] Reimer *et al*., 1993;[156] Ved *et al*., 1996;[160] Weir *et al*., 1993[165]
Halothane ± nitrous oxide	4	Pandit *et al*., 1995;[154] Splinter *et al*., 1995;[158] Crawford *et al*., 1998;[140] Watcha *et al*., 1999[163]
Propofol vs sevoflurane maintenance	2	Gurkan *et al*., 1999;[144] Uezono *et al*., 2000[159]
Sevoflurane vs halothane maintenance	2	Ariffin *et al*., 1997;[138] Viitanen *et al*., 2000[162]

into savings in resource use. Hannallah and co-workers[146] found no reduction in length of stay with propofol.

Inhalational versus intravenous induction
Four studies examined inhalational versus intravenous induction.[144,146,148,161] Kotiniemi and Ryhanen[148] reported a reduction in PONV before and after discharge for halothane over thiopentone. Viitanen and co-workers[161] did not find any differences in PONV before or after discharge or length of stay for propofol and sevoflurane. Hannallah and co-workers[146] reported a reduction in PONV before discharge for propofol versus halothane, but also reported a reduction in PONV after discharge in children induced and maintained with halothane versus propofol. Gurkan and co-workers[144] measured only emesis and the number of occurrences of the oculocardiac reflex during strabismus surgery. They found less vomiting with propofol.

Sevoflurane versus halothane induction
Nine studies examined the use of sevoflurane versus the use of halothane for induction and maintenance.[13,143,147,149,151,153,155,164,166]

Intravenous versus inhalational maintenance
Three studies compared isoflurane with propofol.[141,145,150] Davis and co-workers[141] and Hamunen and co-workers[145] reported no reduction in PONV before discharge. Martin and co-workers[150] measured PONV before and after discharge and reported a reduction in both parameters. Martin and co-workers[150] and Davis and co-workers[141] reported no change in length of stay with the two regimens.

Four studies compared propofol with halothane.[152,156,160,165] Reimer and co-workers[156] reported that, in a study of strabismus patients, the use of propofol with or without the use of N_2O decreased only early emesis when compared with thiopentone or halothane; the overall rate of PONV was not reduced. All studies reported no reduction in PONV before discharge. Moore and Underwood[152] measured the rate of PONV after discharge, and reported no reduction. No studies reported a difference in length of stay. Ved and co-workers[160] found less vomiting with propofol, but no difference in discharge times or admission rates. Weir and co-workers[165] measured only emesis, and found less with propofol.

Different inhalational agents for maintenance

Sevoflurane versus halothane

Eleven studies compared sevoflurane with halothane.[13,138,143,147,149,151,153,155,162,164,166] Only Piat and co-workers[155] did not record PONV before discharge, and only Meretoja and co-workers[151] reported a reduction in PONV before discharge with sevoflurane. Walker and co-workers,[164] Welborn and co-workers[166] and Naito and co-workers[153] recorded the rate of PONV after discharge, and did not find a difference between the two agents. Only Piat and co-workers,[155] Naito and co-workers[153] and Walker and co-workers[164] did not record the length of stay before discharge, and only Meretoja and co-workers[151] reported a reduction, with sevoflurane. Johannesson and co-workers,[147] Lerman and co-workers[149] and Sury and co-workers[13] reported increased emergence agitation with sevoflurane over halothane. Viitanen and co-workers[162] and Ariffin and co-workers[138] found less vomiting and a more rapid emergence with sevoflurane.

Desflurane versus halothane

Two studies compared desflurane with halothane.[141,166] Neither study reported differences in PONV or length of stay with the two agents.

Inhalational versus intravenous agents for maintenance

Propofol versus sevoflurane

Two studies compared propofol maintenance with sevoflurane maintenance.[144,159] Uezono and co-workers[159] found a more rapid emergence and a greater incidence of emergence delirium with sevoflurane. Despite a greater time spent in the postanaesthetic care unit, the patient satisfaction scores for propofol were higher. Gurkan and co-workers[144] only measured emesis and the number of occurrences of the oculocardiac reflex (surgical reflexes resulting in adverse haemodynamic changes), and found less vomiting but more occurrences of the oculocardiac reflex with propofol.

The role of N_2O

Twenty-three of the 28 studies used N_2O in all alternatives. Only Cheng and co-workers,[139] Moore and Underwood,[152] Uezono and co-workers[159] and Splinter and co-workers[158] used anaesthetic techniques in the absence of N_2O. Four studies[140,154,158,163] were found that addressed the impact of N_2O. Splinter and co-workers[158] reported that N_2O did not increase the incidence of vomiting in children undergoing myringotomy, although vomiting increased with age and was associated with an increase in length of stay. Pandit and co-workers[154] measured only the length of stay on the postanaesthetic care unit and vomiting, and found no effect of N_2O on either. Crawford and co-workers[140] reported that N_2O had little effect on the rate of recovery after propofol, but it significantly increased the incidence of PONV. Watcha and co-workers[163] concluded that TIVA with propofol resulted in a more rapid recovery and less PONV than a halothane–nitrous oxide–droperidol regimen.

Impact of age

Some studies reported an increase in PONV with age.[158] Any study examining the impact of anaesthesia on PONV in children will have to take this into account.

Relevance of the clinical evidence to UK practice

Only four studies were from the UK, so different practice patterns in the studies may reduce their relevance to UK practice. However, most studies were grade I RCTs and all were published in the last 10 years, so this may reduce confounders and improve relevance. Desflurane is not used commonly in the UK, but all the other agents are used. Some studies were carried out on strabismus surgery or tonsillectomies, which pose an increased risk of surgically induced complications.

Current issues and uncertainties

This review highlights the following issues and uncertainties:

- The evidence available is primarily from small RCTs concentrating on discharge times and PONV before discharge, with insufficient emphasis on clinical parameters after discharge.
- It is not clear from the evidence which is the optimal agent for induction or maintenance.
- It is not clear whether the use of propofol, rather than inhalational agents, for induction reduces PONV.
- There appears to be no difference in clinical parameters between sevoflurane and halothane, apart from emergence agitation.
- It is not clear that N_2O has any impact on clinical parameters.
- TIVA is not yet standard practice in day-case paediatric anaesthesia.
- The number of drugs available means that most studies cannot be directly compared because they used different combinations of drugs, or because they used the same drugs but given in different ways.

Patient-based outcomes review

This section examines the current status of research on the impact of anaesthesia techniques in day surgery on patient-based outcomes. Thirty-nine adult and 13 paediatric studies were included in the final review, with the following characteristics:

- Adults: 14 comparative studies and 25 descriptive studies in day surgery.
- Paediatrics: two comparative studies in day surgery, two studies comparing day with inpatient surgery, seven descriptive studies in day surgery and two studies in inpatient surgery.

The studies selected for the final review are summarised in appendix 6 (adult patient-based outcomes) and appendix 7 (paediatric patient-based outcomes). A variety of approaches exist to determine patient satisfaction and preferences for healthcare treatments and services.[49] The description 'patient-based outcome measure' is "a short-hand term referring to the array of questionnaires, interview schedules and other related methods of assessing health, illness and benefits of healthcare interventions from the patient's perspective".[49] A wide range of patient-based outcome measures have been used in the studies examined. These are summarised in *Table 5*.

Adult studies

Methods used

Thirteen RCTs and 24 descriptive studies looked at the patient-based differences in recovery characteristics following different anaesthetic agents in day surgery. Sixteen studies were from the UK, five from Sweden, three from Finland, three from Australia, two from Canada, one from Italy, one from The Netherlands, one from Ghana, one from Germany and four from the USA.

The comparative studies involved the following comparisons:

- TIVA versus propofol or thiopentone induction and inhalational maintenance
- propofol and alfentanil versus thiopentone and N_2O
- desflurane versus isoflurane
- propofol versus isoflurane
- propofol/ketamine versus propofol/fentanyl versus thiopentone/fentanyl
- TIVA versus propofol/isoflurane
- sevoflurane versus isoflurane
- general versus local anaesthesia.

Larsen and co-workers[89] evaluated the Perceptive Accuracy Test (PAT) to assess psychomotor recovery following propofol or isoflurane anaesthesia for day surgery. They investigated the suitability of the PAT and found that it is simple, easy to use and reproducible. Other psychometric recovery devices such as the Digit Symbol Substitution Test (DSST),[108,189] the Finger Tapping Test[79] and the Mood Adjective Checklist (MACL)[78,79] have also been used to assess recovery. Outcome measures that quantify patients' experience of pain are used regularly.[78,171,189,210]

One comparative study[197] looked at long-term clinical outcome by using the standardised Cognitive Failure Questionnaire (CFQ). The study investigated cognitive function for 3 days postoperatively in those patients who received a general anaesthetic and compared this with the cognitive function of patients who received a local anaesthetic for their day-case procedures. The study found that in the 3-day period after discharge patients who had general anaesthesia experienced a significant increase in cognitive failures compared with their preoperative baseline scores. Unfortunately, in this study the day-surgery procedures were not similar in the general anaesthetic and local anaesthetic patients.

Most studies assessed 'patient satisfaction'. There are a number of descriptive studies, surveys and audits of satisfaction in day patients.[19,168,172,178,180,181,183,196] Telephone surveys to look at patient satisfaction with day-surgery services have also been carried out.[185]

Clinical audits are common in day-case practice to assess patient satisfaction with overall services and consider improvements. Minor postoperative complications are important to patients and represent areas for potential improvement in anaesthetic, surgical and nursing care.[188] For instance, if the results of an audit show that patients are not satisfied with pain relief, the pain relief regimen should be re-evaluated.

The largest UK study is that by Black and Sanderson,[169] who were commissioned by the Audit Commission to develop a questionnaire for eliciting patients' preferences. The resultant questionnaire was based on a review of 25 questionnaires on patients' experiences, five of which had been specifically designed for day-surgery patients. The questionnaire has 28 precoded questions plus opportunities for qualitative comments. A slightly modified version was developed for those under

TABLE 5 *Summary of outcome measures in the reviewed literature*

Outcome measure	Description	Studies
Cognitive Failure Questionnaire (CFQ)	25 questions about lapses; used to show differences between before and after	Tzabar *et al*., 1996[197]
Post Hospital Behaviour Questionnaire (PHBQ)	Assesses behaviour changes in 28 items in six categories using a scoring system 1–5, with 1 = 'much less than before' and 5 = 'much more than before'	Kotiniemi *et al*., 1996,[201] 1997;[202] Payne *et al*., 1992;[203] Vernon *et al*., 1996[208]
Mood VAS	10 cm scale consisting of opposite feelings expressed as 'mood' on either side of the VAS. Three factors: alertness, contentedness and calmness. The larger the score, the more alert, content or calm	Gupta *et al*., 1992[79]
VAS baseline assessment of mental state	Scores measured for the subjective variables, such as: asleep–wide awake, no energy–full of energy, confused–clear headed, calm–excited, clumsy–well coordinated, no nausea–worse nausea, and no pain–worst pain imaginable	Philip *et al*., 1996[108]
Perceptive Accuracy Test (PAT)	Two-digit numbers are flashed on a colour screen for 225 ms. The subject perceives the displayed number and presses the corresponding number on the numerical display on the computer. A total period of 120 s is given to recognise as many numbers as possible	Gupta *et al*., 1996;[79] Larsen *et al*., 1992[89]
Digit Symbol Substitution Test (DSST)	The subject is asked to place random digits from 0 to 9 by a symbol which is given in the test paper. The score is calculated as the number of correctly substituted digits in 120 s	Philip *et al*., 1996;[108] Nelskyla *et al*., 1997[189]
Finger Tapping Test	The subject is asked to press a keypad as many times as possible in 20 s. The number of times the pad is pressed is taken as the subject's finger tapping score	Gupta *et al*., 1996[79]
Mood Adjective Checklist (MACL)	A questionnaire which looks at six dimensions of mood: hedonic tone (troubled or cheerful), extroversion (withdrawn or outgoing), social orientation (cross or cooperative), activity (indifferent or enthusiastic), calmness (strained or relaxed) and control (restrained or self-assured) Ratings are made on a scale of 1 to 4 (1 = negative attribute; 4 = positive attribute)	Gupta *et al*., 1995,[78] 1996[79]
PONV	PONV is graded in four categories: (1) no nausea or mild nausea (duration less than 10 min); (2) prolonged nausea (duration more than 10 min); (3) retching; (4) vomiting	Nelskyla *et al*., 1997[189]
VAS pain scores	Pain assessed using a 0–100 mm scale where 0 = no pain and 100 mm = severe pain	Gupta *et al*., 1995;[78] De Amici *et al*., 2000;[173] Nelskyla *et al*., 1997;[189] Wilson and Doyle, 1996[210]
Eleven-point rating scale	A scale for rating pain and nausea: 0 = no nausea; 10 = worst possible nausea; 0 = no pain; 10 = worst possible pain	Kangas-Saarela *et al*., 1999[183]
Verbal rating score	For rating postoperative pain or nausea. Four categories: none; mild; moderate; severe	Biemans *et al*., 1998[168]

continued

***TABLE 5* contd** *Summary of outcome measures in the reviewed literature*

Outcome measure	Description	Studies
Objective pain score	A pain score based on observations of behaviour and features of facial expression such as crying, movement, agitation, posture and verbal. Following observation, a score of 0–2 is given	Wilson and Doyle, 1996[210]
Four-point numerical pain scale	A pain score based on a four-point self Likert scale, where 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain	Wilson and Doyle, 1996[210]
Trieger Dot Test	The subject joins together a dotted line, which is represented in the form of a figure. The test is performed preoperatively and at 30 and 60 min after the end of anaesthesia. The score is the number of dots missed	Gupta *et al.*, 1995[78]
Preoperative anxiety score (VAS)	A 100 mm non-graduated VAS graded from not anxious at all (0 mm) to very anxious (100 mm)	Brandner *et al.*, 1997[170]
Anxiety	State–Trait Anxiety Inventory. This study used the state form only. The questionnaire contained 20 statements, evenly divided between anxiety-present and anxiety-absent items	Winwood, 1993[198]
Hall and van der Castle Emotions Scale	Any of the following feelings present: angry, apprehensive, happy, sad and confused (with 'sexual feelings' added by authors)	Brandner *et al.*, 1997[170]
Bodily and biological states	Experienced any of the following: sick, hungry, high, sedated, dizzy, light-hearted (with 'headache' added by authors)	Brandner *et al.*, 1997[170]
Aldrete recovery score	A postanaesthesia recovery score looking at: activity, respiration, circulation, consciousness and colour. A rating of 0, 1 or 2 is given to each sign, with a score of 10 indicating a patient in the best possible position	Philip *et al.*, 1996[108]
Postoperative clinical anaesthesia outcomes	Simple descriptions of clinical outcomes: nausea; recall without pain; gagging on endotracheal tube; shivering; vomiting; residual weakness; somnolence; sore throat; normal; pain	Macario *et al.*, 1999[186]
Quality of recovery score (QoR-40)	A 40-item quality of recovery score; identified to represent aspects of good-quality recovery after anaesthesia and surgery. Evaluated at: emotional stage; physical comfort; psychological support; physical independence; pain	Myles *et al.*, 2000[187]
Contingent valuation	The degree of preference for one alternative healthcare intervention is valued using willingness to pay. This equates to the maximum amount of money that must be taken from an individual to equalise a utility change	Hawksworth, 1996;[21] Elliott *et al.*, 2000[33]
Short Form with 36 items (SF-36)	A generic quality of life questionnaire with eight domains	Baker *et al.*, 1995[167]

16 years of age. The study validated this questionnaire and the initial results suggested that patient satisfaction is most affected by age, gender and type of surgical procedure. During 1991–92 the questionnaire was used in 1741 day-surgery patients undergoing day surgery at 11 hospitals in England. Issues relating to anaesthesia included in the questionnaire were: satisfaction with 17 specific aspects of care (not detailed), pain during the first 24 hours, time taken convalescing, impact on activities of daily living, effect of the operation on day-to-day life, speed of recovery, readmission, and use of ambulatory and domiciliary services. Response rates ranged from 33% to 90% (mean 60%). The procedures carried out were: dilatation and curettage (D&C) (12.4%); removal of skin growth (9.4%); cystoscopy (7.9%); dental extraction (7.6%); laparoscopy (7.4%); and varicose vein surgery (6.6%). Eighty-four per cent of patients would recommend day surgery in similar circumstances, reflecting the generally high levels of satisfaction in this area.

The use of satisfaction as an outcome in clinical or economic evaluations is problematic due to the range of methods available to measure it, but more specifically because an 'index' of satisfaction is required for analysis. There is little evidence of the development of this type of measure in anaesthesia in general. One descriptive study was found that developed a CV method in the form of a willingness-to-pay tool.[21] The tool had been developed in anaesthetic staff rather than patients, because it was rejected by three ethics committees as too politically sensitive. A further study looked at 80 patients' valuations to reduce the incidence of PONV to zero.[176] The willingness-to-pay values were found to be in the range US $56–100. The study did not explore any of the methodological issues associated with the development of valid CV instruments. Elliott and co-workers[33] explored the methodological development of a CV tool to elicit patients' preferences and willingness to pay for alternative anaesthetic agents in day surgery. The willingness-to-pay values for induction agents were a mean of £208 for propofol and £105 for sevoflurane. The mean willingness-to-pay value for maintenance with propofol was £157.

In another descriptive study, Macario and co-workers[186] undertook a survey to try and quantify patients' preferences for postoperative anaesthesia outcomes by asking them to rank ten possible postoperative outcomes. Patients rated the most undesirable as being vomiting, gagging on the tracheal tube and incisional pain. The authors felt that patient validation of different outcomes was necessary for economic studies in anaesthesia.

Baker and co-workers[167] used the Short Form with 36 items (SF-36) to measure health status in varicose vein day surgery. The SF-36 scores indicated that the operation caused increased pain and reduced role function at 1 month. At 6 months all dimensions except social function and health perception were improved.

No other studies were found that evaluated the use of utility measures, such as QALYs. However, this is not surprising, as patient-based differences between anaesthetic techniques are transient and 'process-orientated'. Therefore, outcome-oriented measures such as QALYs will not be sensitive to these differences.

Qualitative studies are often useful in providing an in-depth analysis of patient satisfaction. One such study, using a grounded theory methodology, explored patients' experiences and views of day surgery which would lead to improving the quality of this service. This study highlighted the need for adequate preparation and provision of information for patients attending for day surgery.[191]

In summary, in the small number of studies found, a wide range of methods was used, but reported in little detail. They were mostly unvalidated, apart from the CFQ and the Aldrete recovery score, and were used in small groups of patients. Further work is required to satisfy the criteria for the evaluation of outcomes measures suggested by Fitzpatrick and co-workers.[49]

Results of studies

High levels of satisfaction with the day surgery process overall were reported by patients.

Two studies reported a higher incidence of 'dreams' with propofol,[164,180] although one of these studies[180] also used ketamine. Brandner and co-workers[170] reported that patients 'felt happier' with TIVA than with thiopentone induction or isoflurane maintenance ($p = 0.0038$). Gupta and co-workers[78] reported no mood difference between patients maintained with propofol or isoflurane. Larsen and co-workers[89] reported quicker psychomotor recovery with isoflurane than with propofol ($p < 0.05$), as did Nelskyla and co-workers[189] ($p < 0.05$). Philip and co-workers[108] reported faster cognitive recovery with sevoflurane than with isoflurane ($p < 0.001$).

No studies followed up these results after discharge to examine whether there were any real differences from the patient's perspective.

It is clear from this review that researchers and clinicians believe cognitive failure is the most important patient-based outcome for investigation. However, it is not clear whether patients are of the same view. In-depth interviews with day-surgery patients suggest that the mode of anaesthesia and the recovery profile are not patients' principal areas of concern.[191] In the descriptive studies the issues addressed were principally PONV and pain, but it is not clear whether the patients or the researchers had set this agenda.

Paediatric studies

Methods

Four RCTs and nine descriptive studies were included in this review. The Post Hospital Behaviour Questionnaire (PHBQ) developed by Kotiniemi and co-workers[202] is the method primarily used to assess the impact of anaesthesia on paediatric patient-based outcomes. It is widely used in behavioural paediatrics. The PHBQ consists of 28 items used by parents to judge the impact of hospitalisation on their child's behaviour. It has been used extensively by child psychologists to assess the impact of psychological therapy on ameliorating the psychological effects of hospitalisation.[208] It is suggested that this method is reliable, valid and sensitive to subtle changes in children's behaviour, although it is also sensitive to the questionnaire format, the study design, the subject's age and the length of hospitalisation. The PHBQ was used in the two paediatric RCTs that evaluated the effect of different anaesthetic interventions, in order to assess changes in a child's behaviour.[201,203] It was also used in three of the descriptive studies.[99,148,208] One further study developed a paediatric pain score for use by parents.[210]

The types of surgery examined were day and inpatient surgery, and some studies also included medical patients. The ages of patients ranged from 4 months to 13.4 years. The length of assessment was usually 2 weeks to 1 month, with some studies looking at changes up to 3 months. The comparative studies compared the following alternatives:

- inpatient versus day surgery
- thiopentone versus halothane versus rectal methohexitone for induction
- premedication regimens versus no premedication.

Results

In a small RCT, Payne and co-workers[203] looked at behavioural changes in children following minor surgery in four comparable groups receiving different premedication. The parents assessed behaviour 2 weeks postoperatively. The study found that intravenous or oral midazolam provided some benefit to the child with behavioural changes, such as night crying being less frequent or severe. A small RCT by Kotiniemi and co-workers[201] evaluated a child's behaviour at 1 day, 1 week and 1 month while investigating three different anaesthetic induction agents (intravenous thiopentone, inhalational halothane and rectal methohexitone). The study showed that there was no statistically significant difference between the groups in the proportion of children who showed postoperative behavioural problems, although there was a trend to those children receiving inhalational induction having more negative memories of anaesthesia.

Three descriptive studies used the PHBQ to evaluate a child's behaviour following day surgery.[148,200,208] Multiple regression analysis revealed that the principal factors affecting the behaviour reported by parents were pain at home, PONV in hospital, age more than 5 years and the administration of postoperative opioids.[202] Kotiniemi and co-workers[202] suggested that pain and other unpleasant experiences in hospital predict the occurrence of behavioural problems up to the fourth week.

Vernon and co-workers[208] recognised that a combination of illness and hospitalisation is a psychologically upsetting experience for children in general, resulting in increased separation anxiety, increased sleep anxiety and increased aggression toward authority. Furthermore, a survey done in the UK by Selby and co-workers[205] revealed a higher incidence of minor morbidity following day surgery than had been previously reported when 266 children (aged 5 years and over) were interviewed by an anaesthetist regarding minor sequelae after day surgery. This suggests that the trauma that children experience during hospitalisation may not be detected by studies using clinicians', nurses' or parents' assessments of their experiences.

A survey by Sikich and co-workers[206] evaluated parental perceptions, expectations and preferences for postanaesthetic recovery of children. They highlighted that parents were concerned about the level of pain and vomiting postoperatively. Speed of discharge was not viewed as a high priority for parents.

No studies addressed the issue of parents assessing their children's quality of life or preferences, and thus in effect eliciting proxy rather than true values.

This section of the review shows the inadequate quantity and quality of research on paediatric patient-based outcomes in day surgery. However, the studies that were found suggest that the PHBQ is an appropriate paediatric patient-based tool. This questionnaire has been validated extensively and, with a large enough patient-group, it is believed to be sufficiently sensitive to pick up differences caused by different anaesthetic regimens. No studies were found that looked at the use of utility measures such as QALYs or patient preferences via the use of CV. However, this is not surprising. Also, the methodological difficulties of eliciting utilities or CVs for paediatric interventions are surpassed only by the ethical sensitivity of research in this area.

Summary

There is currently no reliable evidence that identifies whether differences in patients' satisfaction, preferences or self-assessed quality of life are caused by different anaesthetic techniques. From the evidence available it is not possible to state which are the optimal induction or maintenance anaesthesia techniques for day-surgery patients. Most of the studies carried out are from the UK, and so are relevant to UK practice. The tools used in the adult studies are wide-ranging, are generally unvalidated (apart from the CFQ and SF-36) and are rarely used beyond hospital discharge. The paediatric studies used the PHBQ, a validated tool that is sufficiently sensitive to detect differences in anaesthetic agents. There are no comparative studies of paediatric day-surgery anaesthesia in the UK.

Costs and cost-effectiveness of anaesthesia

Ninety-nine studies (*Table 6*) were originally retrieved from the economic literature and screened. Most of these (75%) were excluded. Nine of the excluded papers (12%) were reviews of existing literature, which were not based on systematic search and review methods, or discussion papers. Ten papers (14%) only reported data on anaesthesia for inpatient surgery. Seventeen papers (23%) did not include an evaluation of anaesthetic techniques, procedures or agents or include relevant data. Thirty-eight papers (52%) did not contain sufficient information to identify data that were specific to anaesthetic techniques, procedures or agents in general anaesthesia.

Thirteen of the included papers (58%) were formal cost or economic comparisons of anaesthetic techniques, procedures or agents.

Characteristics of included studies

The characteristics of the 20 included cost or economic studies that included direct comparisons of anaesthetic agents are summarised in appendix 8. Half of the papers were defined by the authors as cost-effectiveness or cost–benefit studies, and were categorised as full economic evaluations for descriptive and quality assessment purposes. In addition, four studies[23,126,211,218] did not include a direct comparison of anaesthetic agents, but did include cost evaluations of surgical procedures and organisation of care and the potential impact on costs of reducing the incidence of adverse anaesthetic outcomes.

Propofol was included in the majority of these evaluations (95%), sevoflurane in 45% and thiopentone in 45%. Other agents included in the evaluations were desflurane (20%), isoflurane

TABLE 6 *Summary of the cost or economic studies screened*

Cost or economic studies	No. of studies	
	Primary evaluation of anaesthetic technique or agents	Other
Papers retrieved and assessed	67	22
Papers excluded	35	39
Papers reviewed	20	4
Formal economic evaluations:		
as defined by the authors	8	1
meet economic evaluation criteria	0	0

(30%) and methohexitone (5%). The main justifications given for the alternatives and comparison were the differences in the relative acquisition price and associated hospital costs between the agents. Typically, the newer anaesthetic agents, such as propofol, sevoflurane and desflurane, were described as potentially being of higher cost. This was used as a justification for including them in the evaluations.

Quality assessment

The type of evidence and the quality assessment of the included cost and economic evaluations of specific anaesthetic agents are summarised in appendix 9. All the studies, except four which used a cohort design, were based on data collected on patients enrolled in RCTs. None of these evaluations could be categorised as well-controlled RCTs due to inadequate concealment of the allocation or randomisation method and inadequate reporting methods. None of the included papers satisfied the criteria for adequate or good cost or economic studies in all the categories.

Issues about the design of cost or economic comparisons that were common to all the papers included:

- The viewpoint or perspective of the study, against which the range of included costs and outcomes could be assessed, was not specified.
- There was inadequate or no justification of the alternatives included, or the form of evaluation used.
- Descriptions of the methods used to measure and value resource use were inadequate.
- Inadequate information was given about the currency and price data used, the year to which the data pertained and the methods used to adjust price data for inflation or currency conversions.
- There was a lack of justification for the limited time horizon and the range of resource use and cost measures used.
- Information on the time horizon for the measurement and valuation of resource use and about outcomes and the need for discounting was inadequate.
- There was no sensitivity analysis to evaluate uncertainty in the results, which could not be assessed by statistical analysis (e.g. sources of price data, range of costs included, use of charges rather than opportunity costs).
- There was inadequate consideration of sample size and power calculations for economic variables.

None of the evaluations defined by the authors as economic analyses specified the primary outcome measure used for a comparison of the costs and effects or reported an incremental comparison of costs and outcomes.

A summary of the type of evidence and the quality assessment of the four evaluations that were not specific to anaesthetic agents is given in appendix 9.[23,126,211,218] Three of these were formal cost or economic comparisons of surgical procedures or other interventions. As with the evaluations of anaesthetic agents, these studies did not meet the criteria for well-controlled randomised trials or adequate cost or economic comparisons.

Cost results

Propofol

Of the 19 studies that included propofol as one of the primary interventions,[28,29,84,86,99,125,174,212–223] 17 suggested that this agent was associated with a higher cost than the other primary agents included in the analysis. One study found sevoflurane and one found thiopentone to be of higher cost than propofol.

Sevoflurane

Overall, sevoflurane was associated with lower costs than propofol (four studies), but higher costs than desflurane (two studies), isoflurane (two studies) or thiopentone (one study).

Thiopentone

Thiopentone was associated with lower costs than propofol (seven studies) and sevoflurane (one study). Thiopentone was found to be of higher cost than propofol in one study.

Desflurane

Desflurane was compared to propofol (three studies).[84,213,216] In all the evaluations, desflurane was associated with lower costs than the alternative anaesthetic agent.

Isoflurane

Isoflurane was compared to sevoflurane (two studies),[219,224] propofol (one study)[213] and desflurane (one study).[213] Isoflurane was the lower cost agent in all the studies.

Other evaluations

The results of the other evaluations suggest that the anaesthetic agent had little impact on the use of resources such as operating theatre or recovery room time. In addition, one study indicated that eliminating adverse anaesthesia outcomes had little impact on the total costs of surgery.

Clinical effectiveness

The authors concluded that propofol was superior to the alternative anaesthetic agent in 11 of the 19 evaluations that included it (versus thiopentone three studies, versus sevoflurane four studies, versus desflurane one study, versus isoflurane one study). No differences were indicated between any of the other agents evaluated.

Cost-effectiveness

None of the studies calculated incremental cost-effectiveness ratios (ICERs). One study reported the cost per complete satisfaction with treatment.[129] Propofol was found to be cost saving and associated with better recovery times in one study (versus thiopentone), and cost additive with superior effectiveness in ten studies. The gains in effectiveness were not valued in comparison to the additional cost to assess whether the higher cost of propofol was worthwhile. The higher costs associated with sevoflurane and its similar effectiveness suggest that this agent may be less cost-effective that desflurane, thiopentone or isoflurane.

Summary

The results of the economic literature review suggest that propofol and sevoflurane may be of higher cost than thiopentone, desflurane and isoflurane. However, the review also indicated that there were problems with the quality of the design and the breadth of costs and outcomes considered in all the studies. This means that the robustness of the results and the conclusions about the relative costs and cost-effectiveness is uncertain and based on limited information.

Summary

This review highlights the issues and uncertainties described below.

Clinical outcomes

A large quantity of high-quality published evidence on clinical outcomes was available. The variety of agents and techniques used limited comparison to some extent.

- The evidence available is primarily in the form of small RCTs concentrating on discharge times and PONV before discharge, with insufficient emphasis on clinical outcomes after discharge.
- It is not clear which is the optimal agent for induction or maintenance.
- It is not clear whether the use of propofol for induction reduces PONV over inhalational agents, although propofol is superior to thiopentone in this respect.
- There appears to be no difference in clinical parameters between sevoflurane and halothane for induction in children, apart from emergence agitation.
- There appears to be no clear optimal inhalational agent for maintenance of anaesthesia.
- The induction agent appears to have more impact on recovery than does the maintenance agent.
- The use of propofol in TIVA reduces PONV rates compared with other anaesthetic combinations.
- It is not clear that N_2O has any impact on clinical parameters.
- TIVA is not yet standard practice in adult day-surgery anaesthesia, and is hardly emerging in paediatric anaesthesia.
- Different patient groups and different types of surgery led to different base rates in PONV, and the range of anaesthetic techniques had different effects on clinical outcomes.

Patient-based outcomes

- There is currently no reliable evidence that identifies whether differences in patients' satisfaction, preferences or self-assessed quality of life are caused by different anaesthetic techniques.
- Most of the studies were carried out in the UK, and so are relevant to UK practice.
- The tools used in the adult studies are wide ranging, generally unvalidated (apart from the CFQ and SF-36) and are rarely applied beyond hospital discharge.
- CV has been used to evaluate associated anaesthetic techniques, but is still under methodological development.
- The paediatric studies used the PHBQ, a validated tool that is sufficiently sensitive to detect differences in anaesthetic agents. There have been no comparative studies of paediatric day-surgery anaesthesia in the UK.
- From the evidence available it is not possible to state which are optimal induction or maintenance anaesthesia techniques for day-surgery patients.

Costs and cost-effectiveness

- From the evidence available it is not possible to state which are optimal induction or maintenance anaesthesia techniques for day-surgery patients.
- The results of the economic literature review suggest that propofol and sevoflurane may be of higher cost than thiopentone, desflurane and isoflurane.

- There are problems with the quality of the design and the breadth of costs and outcomes considered in all the studies. This means that the robustness of the results and conclusions about the relative costs and cost-effectiveness is uncertain and based on limited information.

Chapter 3

National survey of anaesthetic practice for paediatric and adult day surgery

Introduction

Day-case surgery is responsible for an increasing proportion of the surgery performed each year.[229] The benefits to the patient are the avoidance of a hospital admission and minimal disruption to their lifestyle. To achieve rapid discharge from hospital, debate has surrounded how best to avoid post-operative morbidity (e.g. pain, nausea and vomiting). For this reason, the choice of anaesthetic agent, technique and personnel has been seen as critical.[1,144]

The literature review (see chapter 2) reports published practice patterns, variations and trends for adult and paediatric anaesthetic practice. The aim of the present survey was to inform the investigators of the anaesthetic agents and techniques in common use in paediatric and adult day surgery in the UK. The national survey also provided data for the economic analyses, which were specified in the economic evaluation protocol. The main areas explored were: premedication; induction; maintenance; prophylactic and treatment anti-emetics; analgesia; local anaesthesia; and duration of day-case procedures. This information was used to inform the development of the sensitivity analysis, to model the impact of using other anaesthetic techniques and to extrapolate the results of the evaluation in context with current clinical practice in the UK.

Method

The specific objectives of the national survey were:

- to provide a range of estimates for the duration of procedures in the selected areas of day surgery
- to characterise the use of premedication agents, induction and maintenance agents, low flow rates, prophylactic anti-emetics, intraoperative analgesia, local anaesthetics, suxamethonium and non-depolarising neuromuscular blocking agents
- to elucidate the treatment of PONV.

Preliminary survey

In January 1999, a preliminary survey of paediatric anaesthetic practice was conducted to inform the choice of alternative anaesthetic agents for the arms of the paediatric empirical study. Twenty-nine consultant anaesthetists from 11 specialist paediatric hospitals were surveyed. The response rate was 90% (n = 26). The majority (80%) of these anaesthetists used propofol as their usual choice for the induction of anaesthesia. Eight per cent reported using sevoflurane for induction. A large number of anaesthetists used isoflurane (64%) or halothane (24%), with or without N_2O, and a small number (8%) of anaesthetists used sevoflurane for the maintenance of anaesthesia. The results of this preliminary survey were combined with the findings from the literature review (see chapter 2) to define the selected alternative anaesthetic agents in the paediatric empirical study.

National survey

The national postal survey used a structured data collection instrument comprising closed questions about key aspects of anaesthetising a patient for day surgery (see appendix 11). These questions were formed from the results of a pre-pilot survey of paediatric anaesthetic practice. The structured questionnaire was then piloted in a sample (n = 19) of consultant anaesthetists based in one of the NHS trusts involved in the empirical study. The pilot survey generated a 90% response rate and worked extremely well. No changes were made to the survey instrument.

It was assumed that answers to the survey questions would be procedure specific, and so selected areas of day surgery and examples of procedures were selected in order to focus anaesthetists' responses. This means that the results will not be generalisable to all types of day surgery, as the answers are specific to the named types of operations. The selected areas of day surgery matched those included in the empirical study. These areas were urology (e.g. cystoscopy) and orthopaedics (e.g. knee arthroscopy) for adult practice, and general surgery (e.g. circumcision) for paediatric practice. Simpson and Russell's[32] survey of anaesthetic practice summarised the main approaches used to anaesthetise patients for day-case gynaecological laparoscopy, and this procedure type was not represented in our survey.

Survey sample frame

In October 2000, consultant anaesthetists involved in anaesthetising patients for day surgery in NHS trusts in the UK were contacted via a list of clinical directors of anaesthesia (n = 270). This list had recently been used in a survey of clinical directors.[230]

Analysis

Frequency data and descriptive statistics were produced for three main sections, which corresponded with the three clinical areas: urology, orthopaedics and paediatrics. SPSS version 9® was the statistical software package used.

Answers were coded as 'not appropriate' if the respondents indicated they were not involved in treating day patients from one of the specified clinical areas and then went on to leave the relevant questions in the survey blank.

Respondents were asked to name the agent they used routinely for each stage of the anaesthetic process. In some cases respondents named more than one agent. The purpose of the survey was to determine the popularity of the available anaesthetic techniques and so, if more than one agent was named, the response was weighted by the number of responses offered. The number of responses for each named agent are therefore presented and converted to a percentage of the sample size.

Results

The results are presented in four main sections relating to duration of day procedures, use of premedication, general anaesthesia and perioperative supplementary therapy.

Response rate

The overall response rate to the main survey was 76% (n = 204). Five of the returned questionnaires were not completed. A total of 199 (74%) completed questionnaires were included in the analysis.

The completed questionnaires were representative of all UK NHS regions (including Northern Ireland, Scotland and Wales). Respondents seemed interested in the topic area and 68% of them indicated that they would like a summary of the results and wrote additional comments at the end of the questionnaire describing their current practice or making suggestions about the implications of the study.

All respondents were consultant anaesthetists and 94% of them said that their base hospital had a dedicated day-case ward or unit. Not everyone who completed a questionnaire worked in all the three areas of day surgery, 15% did not work with urology or paediatric day-surgery patients and 9% did not work with orthopaedic day-surgery patients. As anticipated, most respondents who indicated that they did not do any urology, orthopaedic or paediatric day surgery did not complete the relevant sections of the questionnaire. Some respondents did complete the sections for urology and orthopaedics (3% and 2%, respectively) even though they stated they did not have any day patients from these clinical areas. These responses were included in the analysis.

Duration of day-case procedures

The mean duration of a day-case procedure was reported to be 26 minutes (95% confidence interval (CI), 21.7 to 30.2; n = 170) for urology, 41 minutes (95% CI, 37.2 to 45.7; n = 181) for orthopaedics and 34 minutes (95% CI, 29.3 to 39.1; n = 167) for paediatrics. The standard accepted maximum for a day-case operation is 60 minutes,[3] but seven respondents reported the remarkably long time of 240 minutes. It is possible that these seven respondents may have misunderstood the question and estimated the total time a person having day surgery stays under the care of the hospital rather than estimating the length of time to complete the day-case procedure.

Use of premedication

The majority of respondents indicated that they did not give premedication for urology (83%), orthopaedics (81%) or paediatrics (67%). Respondents were asked to indicate 'In what percentage of your day-case patients do you routinely use premedication?'. Respondents said that premedication would be used routinely in 6% (95% CI, 2.7 to 8.4; n = 173) of their urology day-case patients, 12% (95% CI, 7.8 to 16.1; n = 185) of their orthopaedic day-case patients and 19% (95% CI, 13.6 to 23.9; n = 167) of their paediatric day-case patients. *Table 7* summarises the named premedication agents of choice used in day surgery.

General anaesthesia

Induction

Propofol was the most popular induction agent used routinely for day surgery in all three clinical areas (*Table 8*). Sevoflurane was a popular choice for paediatric day surgery, but not for adult urology or orthopaedic day surgery. Some of the respondents (12% for urology, 14% for orthopaedics, 35% for paediatrics) named more

TABLE 7 *The premedication agents of choice in day surgery*

Premedication agent	Respondents (%)		
	Urology	Orthopaedics	Paediatrics
Benzodiazepine	2	2	8
NSAID or paracetamol	2	8	9
Any combination of NSAID, anti-emetic or H_2-antagonist	1	4	0
Topical anaesthetic	0	0	5
Trimeprazine	0	0	0.5

TABLE 8 *Named induction agents used routinely for day surgery in the three specified clinical areas*

Induction agent	Respondents (%)		
	Urology	Orthopaedics	Paediatrics
Propofol	89	86	60
Propofol and midazolam	6	9	2
Sevoflurane	2	1	28
Thiopentone	0.3	0	7
Propofol and midazolam and opioid	1	1	0
Sevoflurane and midazolam	0.3	2	0.6
Etomidate	1	0.3	0
Propofol and opioid	0	0.6	0.6
Thiopentone and opioid	0	0	0.6
Etomidate and midazolam	0.3	0	0
Thiopentone and midazolam	0	0	0.6
Isoflurane	0	0	0.3

than one agent, and these responses were weighted accordingly. In some cases respondents referred to using a benzodiazepine, such as midazolam, with a general anaesthetic to reduce the dose required for induction of anaesthesia, and this is recorded in *Table 8*.

Respondents were asked to state the dose of induction agent (in milligrams per kilogram body weight) or the concentration of volatile induction agent used. Some respondents (34% for urology, 34% for orthopaedics, 14% for paediatrics) stated a dose range. If respondents stated a range then a variable was created to represent the 'average dose', which was the midpoint of the stated range. If the propofol dose was stated as a single milligram dose (8% for urology, 7% for orthopaedics) then the average weight of an adult of 70 kg was used to calculate a milligram per kilogram dose. Two per cent of respondents stated a paediatric propofol dose as a single milligram dose, and these responses were excluded because it is not practical to assume an average weight for a child in the age range 3–12 years. One response for urology and orthopaedics was excluded because the dose range was not legible.

In 7% of urology and 8% of orthopaedic responses, the propofol dose was stated as 'TCI' (target controlled infusion) or propofol was stated as the anaesthetic agent of choice for induction and maintenance, thus making an estimation of the induction dose difficult. The range of values provided by this sample of respondents was 3–12 µg/ml. These values refer to the reading on the target controlled infusion pump rather than the quantity of drug given to the patient, and were excluded when calculating the mean dose of propofol used to induce anaesthesia.

The mean induction dose of propofol used was 2.4 mg/kg (95% CI, 2.3 to 2.6; $n = 115$) for urology and 2.3 mg/kg (95% CI, 2.2 to 2.5; $n = 115$) for orthopaedics. The mean dose of

propofol used to induce anaesthesia for paediatric day patients was 4.0 mg/kg (95% CI, 3.6 to 4.3; $n = 122$). The stated mean concentration of sevoflurane used to induce anaesthesia in paediatric patients was 6.6% (95% CI, 5.6 to 7.7; $n = 20$).

Maintenance

Table 9 shows the most popular maintenance agents used routinely for day surgery. Some of the respondents (4% ($n = 8$) for urology, 6% ($n = 12$) for orthopaedics, 6% ($n = 11$) for paediatrics) named more than one maintenance agent, and these responses were weighted accordingly. The exception to this was the respondent who named remifentanil and propofol. This was recorded separately because remifentanil can be used to reduce the required dose of general anaesthetic.

A number of respondents stated the dose as a range, and these values were converted to a mean maintenance dose (*Table 10*). The adult maintenance dose for propofol was assumed to be the 'target' dose measured in micrograms per millilitre for a controlled infusion. Target controlled infusion pumps cannot be set for paediatric patient characteristics, and so propofol must be given to paediatric patients as a bolus or manual infusion. Here the units used were milligrams per kilogram body weight per hour.

Fresh gas flow rates

Respondents were asked to state the flow rate of oxygen and N_2O used during the induction and maintenance of anaesthesia (*Table 11*). Some respondents stated a flow range, and this was more often the case for the paediatric day-case patients. If respondents stated a range then a variable was created to represent an 'average flow rate', which was the midpoint of the stated range.

Perioperative supplementary therapy in day-case anaesthesia

Prophylactic anti-emetics

The use of prophylactic anti-emetics for day surgery varied slightly between the three clinical areas. In this sample of anaesthetists, no anti-emetic is given prior to the patient complaining of nausea or vomiting by 50% in urology, 44% in orthopaedics and 58% in paediatrics. A minority of the respondents (2% for urology, 4% for orthopaedics) named more than one prophylactic anti-

TABLE 9 *Named maintenance agents used routinely for day surgery in the three specified clinical areas*

Maintenance agent	Respondents (%)		
	Urology	Orthopaedics	Paediatrics
Isoflurane	56	58	54
Sevoflurane	23	24	38
Propofol	13	13	4
Enflurane	4	3	2
Desflurane	4	1	0
Halothane	0	0	0.6
Propofol and remifentanil	0.6	0.6	0

TABLE 10 *Concentrations (%) or doses (μg/ml) of the named maintenance agents*

Maintenance agent	Mean concentration or dose (95% CI; *n*)		
	Urology	Orthopaedics	Paediatrics
Isoflurane	1.5% (1.35 to 1.55; 75)	1.5% (1.40 to 1.58; 82)	1.5% (1.41 to 1.66; 66)
Sevoflurane	2.0% (1.79 to 2.19; 28)	2.0% (1.82 to 2.20; 32)	2.4% (2.13 to 2.72; 50)
Propofol	5.2 μg/ml (3.37 to 6.92; 12)	5.2 μg/ml (3.50 to 6.78; 13)	10.3 mg/kg/h (6.54 to 14.13; 3)
Enflurane	2.3% (1.46 to 3.13; 5)	2.1% (0.00 to 4.22; 3)	2.3% (0.90 to 3.78; 3)
Desflurane	4.5% (3.52 to 5.48; 4)	4% (–; 1)	–
Halothane	–	–	Not known
Propofol and remifentanil	5 μg/ml (–; 1)	6 μg/ml (–; 1)	–

TABLE 11 *Oxygen and N_2O flow rates for induction and maintenance anaesthesia in the three specified clinical areas*

Fresh gas	Mean flow rate (95% CI; *n*) (l/min)		
	Urology	**Orthopaedics**	**Paediatrics**
Induction oxygen	3.9 (3.58 to 4.23; 170)	4.0 (3.64 to 4.26; 180)	3.6 (3.30 to 3.87; 162)
Induction N_2O	3.0 (2.66 to 3.32; 170)	3.0 (2.72 to 3.36; 178)	3.0 (2.68 to 3.31; 163)
Maintenance oxygen	1.3 (1.13 to 1.46; 170)	1.2 (1.10 to 1.37; 178)	1.9 (1.68 to 2.13; 162)
Maintenance N_2O	1.5 (1.34 to 1.75; 170)	1.5 (1.30 to 1.69; 181)	2.3 (2.01 to 2.55; 158)

emetic, and these responses were weighted accordingly. Ondansetron or cyclizine were the most popular prophylactic anti-emetics (*Table 12*).

Local anaesthetics

Respondents were asked to name just one local anaesthetic they used routinely, but some respondents (3% for urology, 4% for orthopaedics, 4% for paediatrics) named two agents. Combinations of local anaesthetic agents included bupivacaine and lignocaine or ropivacaine. Local anaesthetics can be mixed to modify the overall drug mixture profile, to give rapid onset of action with improved duration of action. Topical lignocaine may also be used in combination with a parenteral form of local anaesthetic.

The use of local anaesthetics varied between the three types of day surgery named in the survey, and local anaesthetic use is likely to be specific to the named example of procedure for the type of day surgery (*Table 13*). Bupivacaine was the most popular choice of local anaesthetic, and respondents said they were likely to use concentrations of 0.5% (17% urology, 59% orthopaedics, 23% paediatrics) or 0.25% (7% urology, 14% orthopaedics, 45% paediatrics) for day surgery.

TABLE 12 *Named prophylactic anti-emetic agents used routinely for day surgery in the three specified clinical areas*

Anti-emetic agent	Respondents (%)		
	Urology	**Orthopaedics**	**Paediatrics**
No agent given	55	46	76
Ondansetron	13	18	18
Cyclizine	12	12	5
Droperidol	11	12	5
Metoclopramide	6	9	1
Beta/dexamethasone	1	1	1
Granisetron	2	2	0
Prochlorperazine	0.6	0	0

TABLE 13 *Named local anaesthetic agents used routinely for day surgery in the three specified clinical areas*

Local anaesthetic agent	Respondents (%)		
	Urology	**Orthopaedics**	**Paediatrics**
Not given	57	5	2
Bupivacaine	30	85	93
Lignocaine	6	0.5	2
Bupivacaine with adrenaline	2	8	0.5
Lignocaine gel	5	0	0
Lignocaine with adrenaline	0	1	0
Ropivacaine	0	0	0.5

Use of supplementary anaesthetic techniques

The use of supplementary therapies and techniques for day surgery may be expected to vary from patient to patient. Estimates for the likelihood that an anaesthetist would use prophylactic anti-emetics, local anaesthetics, non-depolarising neuromuscular blocking agents, suxamethonium or laryngeal masks in a sample of the UK population of day patients were used to develop an economic model of how a patient would be anaesthetised for day surgery. Consultant anaesthetists were asked to estimate the percentage of patients in whom they would routinely use each of these therapies or techniques (*Table 14*). Paediatric day patients undergoing circumcision were less likely to be given a prophylactic anti-emetic than were adult day patients undergoing cystoscopy or arthroscopy. Adult day patients undergoing arthroscopy and paediatric day patients undergoing circumcision were more likely to be given a local anaesthetic. There is a small chance of day patients being given a non-depolarising neuromuscular blocking agent or suxamethonium, and a very high likelihood of them having a laryngeal mask inserted.

Intraoperative analgesics

In general, respondents indicated that intraoperative analgesics would be used. Respondents reported that intraoperative analgesics would not be given in 5% for urology, 1% for orthopaedics and 5% for paediatrics. The majority of respondents (73% for urology, 43% for orthopaedic, 50% for paediatrics) followed the survey directions and named just one intraoperative analgesic (*Table 15*). The remaining respondents who answered the question named between two and four analgesics they would routinely use for urology (26%), orthopaedics (59%) and paediatrics (44%). The responses were weighted accordingly, and are shown in *Table 15*. The most popular combination of analgesic was fentanyl and a non-steroidal anti-inflammatory drug (NSAID), such as diclofenac or ketorolac, which 11% of respondents said they used for urology, 31% for orthopaedics and 18% for paediatrics.

Of those respondents who used opioid analgesics, 45% for urology, 54% for orthopaedics and 33% for paediatrics indicated they gave a prophylactic anti-emetic. Of those respondents who used non-opioid analgesics, 26% for urology, 43% for orthopaedics and 26% for paediatrics indicated they gave a prophylactic anti-emetic.

Treatment anti-emetics

Respondents were asked to name their first- and second-line choice of anti-emetic for the treatment of PONV (*Table 16*). One respondent named many agents for the treatment of PONV for urology and orthopaedic patients. It was not possible to read one respondent's named drug. These two answers were excluded from the analysis. *Table 16* summarises the popularity of each type of named anti-emetic as a first- or second-line agent for this sample of anaesthetists. Cyclizine and ondansetron were favourite choices as first- or second-line treatment anti-emetics. Interestingly, a notable number (46%) of anaesthetists did not indicate a second-line anti-emetic for paediatric day patients.

Implications for the empirical study

This survey of anaesthetic practice generated an excellent response rate and represented the views of anaesthetists across the UK. The main areas of day-case anaesthetic practice explored were: premedication, induction, maintenance, prophylactic and treatment anti-emetics, analgesia, local anaesthesia and length of time for day procedures. The probabilities of using the named therapies for

TABLE 14 *Likelihood of using supplementary anaesthetic techniques in the three specified clinical areas*

Anaesthetic technique	Use (%) (95% CI; *n*)		
	Urology	Orthopaedics	Paediatrics
Prophylactic anti-emetic	32 (26.0 to 38.3; 162)	41 (34.7 to 47.0; 176)	24 (18.1 to 29.0; 159)
Local anaesthetic	26 (21.1 to 31.5; 167)	77 (72.5 to 80.9; 183)	80 (75.7 to 83.8; 166)
Non-depolarising neuromuscular blocking agent	4 (2.3 to 5.3; 170)	6 (3.9 to 8.1; 182)	6 (4.1 to 8.0; 165)
Suxamethonium	0.7 (0.4 to 1.0; 172)	0.7 (0.4 to 1.0; 184)	2.5 (1.3 to 3.7; 168)
Laryngeal mask airway	86 (82.3 to 89.1; 171)	93 (91.6 to 95.1; 184)	85 (81.9 to 88.3; 166)

TABLE 15 *Named intraoperative analgesics used routinely for day surgery in the three specified clinical areas*

Analgesic	Respondents (%)		
	Urology	Orthopaedics	Paediatrics
Opioid analgesics			
Fentanyl	50	43	37
Alfentanil	26	13	11
Morphine	1	5	4
Remifentanil	4	2	0.5
Pethidine	1	0.5	5
Tramadol	0	1	0
Diamorphine	0	1	0.6
Cyclimorph	0	0.5	0
Codeine	0.2	0.2	0.3
NSAIDs			
Diclofenac	7	16	25
Ketorolac	6	13	1
Tenoxicam or piroxicam	0.5	2	0
Ibuprofen	0	0	0.6
Other analgesics			
Paracetamol	0	0	5
Ketamine	0	0	1
No analgesic given			
None	5	1	6

TABLE 16 *First- and second-line treatment anti-emetics in the three specified clinical areas*

Anti-emetic	Respondents (%)					
	Urology		Orthopaedics		Paediatrics	
	First-line choice	Second-line choice	First-line choice	Second-line choice	First-line choice	Second-line choice
Ondansetron	23	42	30	42	49	16
Cyclizine	33	16	36	16	21	12
Prochlorperazine	16	8	15	8	7	2
Metoclopramide	11	5	11	4	6	7
Droperidol	4	4	3	4	2	4
Granisetron or tropisetron	1	2	1	0	0	0
Betamethasone or dexamethasone	0.5	2	0.5	0	0.6	0
Normal saline	0	0.5	0	0	0	0
Trimeprazine	0	0	0	0	0	0.5
No treatment	5	21	3	26	12	55

each area of day-case practice were calculated. Estimates for the mean length of a day procedure were also generated. These estimates were used to inform the choice of variables and range of values for the sensitivity analysis and modelling in the empirical study. These findings were assumed to reflect national practice and were used to set the empirical study in context with current paediatric and adult day-surgery anaesthesia.

Summary

The literature review (see chapter 2) reports current practice patterns, variations and trends for adult and paediatric anaesthetic practice. The aim of this national survey was to inform the investigators of the anaesthetic agents and techniques used in common practice for paediatric and adult day surgery in the UK.

Method

In January 1999, a preliminary survey of paediatric anaesthetic practice was conducted to inform the choice of alternative anaesthetic agents for the arms of the paediatric empirical study. A national postal survey, conducted in October 2000, used a structured data-collection instrument comprising closed questions about the key aspects of anaesthetising a patient for day surgery. Information was collected on premedication, induction, maintenance, prophylactic and treatment anti-emetics, analgesia, local anaesthesia and duration of day procedures.

Results

One-hundred and ninety-nine questionnaires (74% response rate), representing all UK health regions, were analysed. Fifteen per cent of respondents did not anaesthetise urology or paediatric day patients and 9% did not anaesthetise orthopaedic day-surgery patients.

The stated mean length of a day procedure was 26 minutes for urological procedures, 41 minutes for orthopaedic procedures and 34 minutes for paediatric general surgical procedures. Respondents reported that premedication, such as a benzodiazepine or a NSAID, would be used routinely in 6% of their urology, 12% of their orthopaedic and 19% of their paediatric day patients. Propofol was the preferred induction agent for 89% of respondents for urology, 86% for orthopaedics and 60% for paediatrics. Isoflurane was the preferred maintenance agent for 56% of respondents for urology, 58% for orthopaedics and 54% for paediatrics. Low flow rates of N_2O and oxygen were used, but not always. Respondents estimated that a prophylactic anti-emetic would be used in 32% of their urology, 41% of their orthopaedic and 24% of their paediatric day patients. Ondansetron was the preferred choice of drug when a prophylactic anti-emetic was given. The use of prophylactic anti-emetics was not confined to those using intraoperative opioids. Respondents reported that a local anaesthetic, such as bupivacaine, was used routinely in 26% of their urology, 77% of their orthopaedic and 80% of their paediatric day patients. A non-depolarising neuromuscular blocking agent was used routinely by respondents in 4% of their urology, 6% of their orthopaedic and 6% of their paediatric day patients. Suxamethonium was used routinely by respondents in 0.7% of their urology and orthopaedic and 2.5% of their paediatric day patients. A laryngeal mask airway was used routinely by respondents in 86% of their urology, 93% of their orthopaedic and 85% of their paediatric day patients. An intraoperative analgesic was not used routinely by 5% of respondents for urology, 1% for orthopaedics and 6% for paediatrics. A variety of analgesics for intraoperative use were described, but fentanyl alone, or with a NSAID, was the preferred choice. Cyclizine and ondansetron were favourite choices as first- or second-line treatment anti-emetics for urology and orthopaedic day patients. Ondansetron was the first-line treatment for paediatric day patients. Fifty-five per cent of respondents did not indicate a second-line anti-emetic for paediatric day patients.

Implications for the empirical study

The findings from this national survey were used to create a national picture of paediatric and adult day-surgery anaesthesia and inform the choice of variables to be used in the sensitivity analysis and modelling for the empirical study (CESA RCT).

Chapter 4

Economic evaluation methods

Aims and objectives

The overall aim of the CESA economic evaluation (hereafter referred to as the CESA RCT) was to provide robust evidence to healthcare professionals and policy makers about the relative costs, patient benefits and acceptability of different anaesthetic agents. The overall aim of the study was to assess the relative cost-effectiveness of different anaesthetic agents in adult and paediatric day surgery.

The principal objectives of the economic evaluation were to:

- identify and value the impact on patients of different anaesthetic agents in day surgery
- identify and value the resource use associated with the use of different anaesthetic agents in day surgery
- assess the relative value for money of the different anaesthetic agents in day surgery.

Research questions

- Were there differences in the clinical process or the impact of the different anaesthetic agents?
- If there were differences in the clinical impact of the different anaesthetic agents, did these translate into economically important differences in patient preferences and valuations of that impact on their health, quality of life and acceptability?
- If there were differences in the clinical impact of the different anaesthetic agents, did these translate into economically important differences in resource utilisation and costs associated with their use?
- Did any differences in patient valuations or costs result in one or more of the different anaesthetic agents dominating other alternatives in terms of:
  - net savings and equivalent or improved patient outcome
  - improved patient outcome, and equivalent cost or net savings
  - improved patient outcome and higher cost, with a lower ICER than other alternatives?

Perspective

The perspective of the study included:

- the NHS, in terms of the direct costs of providing anaesthesia and anaesthesia-related follow-up care
- the patients, in terms of the outcomes and direct costs of anaesthesia and anaesthesia-related follow-up care.

Study design

A prospective RCT design (CESA RCT) was used to compare the clinical effectiveness, patient preferences and costs of the anaesthetic regimens described below. A randomised design was used to minimise selection bias in the allocation of patients to the interventions evaluated. The trial was pragmatic, with active rather than placebo comparisons. A scientific advisory group was set up to advise on all key aspects of project design and execution, advising on problems or conflicts of a technical or scientific nature (see appendix 12).

Masking

It was not possible to mask anaesthetists or patients to the allocation between methods of administration (inhalation or intravenous). It was also not possible to mask anaesthetists to the anaesthetic agent for the treatment allocation. Researchers could not be masked to treatment allocation because they were collecting prospective resource-use information.

The data analysts were masked to treatment allocation until the primary analysis of the clinical outcome (PONV), adverse events, resource use and costs and willingness-to-pay data were completed.

Treatment protocol

A treatment protocol was developed for the adult and paediatric studies (available from the authors on request). This protocol detailed the recruitment and randomisation procedures, inclusion and exclusion criteria, agents and interventions intended for each treatment arm

(including N_2O flow rates, PONV management), and interventions allowed and disallowed by the study (e.g. no use of prophylactic anti-emetics, premedication, suxamethonium or morphine). All adult patients were preoxygenated via a clear, polythene face mask. Some patients had a cannula inserted prior to induction, and some had the cannula inserted after they were asleep, according to the anaesthetist's usual practice. The doses of intravenous and inhalational anaesthetic agents and the technique used for inhalational induction were at the discretion of the anaesthetist. The only constraint on fresh gas flow was that, in adults, the total fresh gas flow was reduced in all patient groups to a maximum of 4 litres after precisely 5 minutes and a maximum of 2 litres after a further 10 minutes. Anaesthetists involved in the study were supported in their use of these protocols by the researchers on site.

Sample size

The principal clinical endpoint was PONV, and it was on this that the power of the study was determined. The adult study was planned to detect a reduction in PONV from 20% to 10% at 80% power using a two-tailed significance test at the 1% level of significance. The stringent significance level was chosen because it was anticipated that there would be multiple comparisons among the four treatment arms. To attain the stated power, 330 patients were required in each treatment arm. The literature review indicated that gynaecological patients may exhibit different characteristics in terms of PONV rates than the other patients included in the study. A power calculation was therefore performed to estimate the minimum number of gynaecological patients required in each of the four study arms. To attain the stated power, 120 gynaecological patients were required in each treatment arm.

The paediatric study was planned to detect a reduction in PONV from 20% to 10% at 80% power using a two-tailed significance test at the 5% level of significance. To attain the stated power, 220 patients were needed in each of the two study arms.

No interim analyses were planned or stopping rules defined. *Post hoc* power calculations for the four variables were conducted to ensure that there was at least 80% power, at the 1% level of significance (5% for the paediatric study) to detect a statistically significant difference.

Patient population

The sample population was drawn from the patient population eligible for any of the day-surgery procedures described below, and who met the anaesthesia-based inclusion criteria for the trial. Surgical categories were selected to reflect the majority of day-surgery activity. Dental and ophthalmic day-surgery categories were excluded due to their specific anaesthetic requirements. Patients undergoing termination of pregnancy were not approached, to avoid causing possible further distress. The adult study included patients aged over 18 years (i.e. able to give consent) who would normally be admitted for day surgery, to produce a sample that was representative of the UK day-surgery patient population. Children aged between 3 and 12 years were included because, at the inception of the study, propofol was not licensed for children under 3 years of age, and children over 12 years of age are both physiologically and psychologically more like adult patients, and are therefore anaesthetised accordingly. Patients expected to receive suxamethonium were excluded because it induces significant postoperative morbidity (myalgia). Patients who received premedication were excluded because this might affect their postoperative recovery.

Inclusion criteria

The inclusion criteria for the study were:

- patients undergoing day surgery in one of the agreed surgical groups and who were under the care of one of the participating anaesthetists
- patients assessed as fit for day-surgery anaesthesia, using the trial centre's usual assessment protocol
- adult patients were aged 18 years or over
- paediatric patients were aged 3–12 years.

Exclusion criteria

The exclusion criteria for the study were:

- patients undergoing termination of pregnancy
- patients expected to receive suxamethonium as part of the anaesthetic technique
- patients receiving sedative premedication.

Adult and paediatric patient populations were studied. The sample population was consecutive patients attending for day surgery between October 1999 and January 2001 at the Wirral Hospitals NHS Trust and Central Manchester Healthcare NHS Trust.

The adult day-surgery procedures were:

- general, including urology
- orthopaedic
- gynaecology.

The paediatric day-surgery procedures were:

- general
- ear, nose and throat (ENT).

Comparators

The evaluation included two patient populations: adult and paediatric. There are differences between the anaesthetic agents and techniques typically used for each of the populations, which were reflected in the study treatment arms evaluated. The comparators in the adult population reflected two main models of practice (propofol followed by isoflurane or sevoflurane) and two emerging models of practice in the UK (total intravenous or total inhalational anaesthesia) (see chapter 2). The comparators in the paediatric study were obtained from the pilot stage of the paediatric survey (see chapter 3) and reflected two main models of practice. There were no comparisons between the treatment arms of the adult population and those of the paediatric population.

The protocol for the dose of anaesthetic, use of other medications and administration was designed to mirror actual practice. The agents and procedures for each treatment arm in the trial based comparisons were, for the adult population:

- TIVA: propofol induction, propofol maintenance.
- Intravenous/inhalational anaesthesia: propofol induction, isoflurane/N_2O maintenance.
- Intravenous/inhalational anaesthesia: propofol induction, sevoflurane/N_2O maintenance.
- Total inhalational anaesthesia: sevoflurane induction, sevoflurane/N_2O maintenance.

The agents and procedures for each treatment arm in the paediatric population were:

- Intravenous/inhalational anaesthesia: propofol induction, halothane maintenance.
- Total inhalational anaesthesia: sevoflurane induction, sevoflurane maintenance.

Time frame

Resource use was measured and valued from admission to day 7 following discharge from the day-case unit. Patient outcomes were measured postoperatively prior to discharge. Patient valuations were obtained at day 7.

Recruitment and randomisation

Local Research Ethics Committee approval and the approval of the appropriate consultant surgeons was obtained before the study commenced. The relevant consultant anaesthetists were recruited to take part in the study.

At least 24 hours before admission, eligible patients received an information sheet on the study. After arrival on the day-case ward, a research nurse reviewed the information with them and obtained written informed consent from the patient or, for paediatric patients, from the parent or guardian. Consent included taking part on the day, access to medical notes and a telephone interview around day 7.

A computer programme produced pseudo-random numbers from which sequences of patient allocations to anaesthetic regimens were generated. Random allocation was such that each study arm had an equal chance of being included. Block randomisation, with randomly varying block sizes, was employed to attain an even balance of allocations among the anaesthetic regimens.

Random allocation to anaesthetic regimen within these categories was further stratified by gender and hospital site, when appropriate. The randomisation categories were:

- gynaecological patients at Wirral NHS Trust (gynaecology Wirral)
- gynaecological patients at Central Manchester Healthcare Trust (gynaecology St. Mary's)
- orthopaedic male patients at Wirral NHS Trust (orthopaedic male)
- orthopaedic female patients at Wirral NHS Trust (orthopaedic female)
- general male patients at Wirral NHS Trust (general male)
- general female patients at Wirral NHS Trust (general female)
- paediatric male patients (paediatric male)
- paediatric female patients (paediatric female).

The lists of random allocations were held at the study office and batches of sealed envelopes labelled numerically and by surgical group were dispatched to the study sites for the adult and paediatric studies. An envelope was opened, in numerical order, by the research nurses after the patient consented to enter the study.

Measures

Primary clinical outcome measure

The literature review (see chapter 2) identified PONV as the most relevant primary clinical outcome measure to quantify the effectiveness of anaesthetic agents for day surgery. PONV was recorded using the following scale: 0, no nausea or vomiting; 1, nausea; 2, one episode of vomiting; 3, multiple episodes of vomiting. PONV was monitored postoperatively in recovery and on the ward. PONV was used to estimate the sample size requirement and as the primary effectiveness measure for the estimation of cost-effectiveness ratios.

Secondary clinical outcome measures

Further clinical outcome measures were also considered. The secondary clinical outcome measures recorded were orientation in the recovery room, time to recovery room discharge, time to readiness for hospital discharge, and overnight stay on the ward. Orientation of the patient when in the recovery area was graded by the recovery staff using predefined categories: alert and awake, agitated and distressed, and drowsy. The time to recovery room discharge and readiness for hospital discharge were collected from the nursing or medical records. If the patient was admitted overnight, the reason for admission and the subsequent duration of admission was recorded. This information was obtained from the relevant ward nursing staff.

The incidence of adverse events in the anaesthetic room, theatre, recovery and on the ward was monitored and collected. The primary adverse events noted in the anaesthetic room were breath-holding, cough, excessive salivation, excitatory movement during induction, hiccough, laryngospasm and pain on injection. Other adverse events were noted and recorded as they occurred throughout the day-patient episode.

Patient preferences

CV was used to determine patient preferences for alternative anaesthetic agents. The CV method is used to elicit values for items not typically traded in private markets, such as health. Valuation is based on the contingency of the hypothetical market for health. The development of any CV tool requires an explicit handling of the development process. The challenge is to construct hypothetical scenarios that are meaningful to the respondent but free from bias. Valuations of willingness to pay can be carried out using open-ended or closed-ended methods. Open-ended methods may produce contradictory answers, protest answers or no answers at all.[231] The CV instrument used in this study was developed in a pilot study (see appendix 13).[34,45,231–240]

The CV pilot study developed and tested the hypothetical descriptive scenarios of the process and outcome of anaesthesia from interviews with 40 female members of the public. The pilot study examined the direction and value of preferences for one alternative anaesthetic agent over another by asking respondents what they would be willing to pay for the preferred option(s). Respondents' understanding of the CV process was checked by asking them to explain the reasons for their preference for one medicine rather than the other. The pilot study confirmed that the majority of respondents (85%) understood the hypothetical scenarios and that the instrument was suitable for use in the empirical study. The values used on the subsequent VAS were developed during the pilot study.

In the empirical study the adult and paediatric patient groups were provided with two scenarios:

- Scenario 1: valuation of inhalational versus intravenous induction (see appendix 14).
- Scenario 2: valuation of inhalational versus intravenous maintenance (see appendix 15).

Scenario 1 described the likely events that the patient would experience if they received propofol (intravenous) or sevoflurane (inhalational) for induction of anaesthesia. The principal differences here were mode of administration and the pain on injection experienced with propofol.

Scenario 2 described the likely events that the patient would experience if they received inhalational (sevoflurane or isoflurane) or intravenous (propofol) maintenance anaesthesia. The principal difference between the agents and techniques described was the difference in the risk of PONV.[176]

The differences in risk of PONV were based on quantified reductions in the risk of PONV in order

to provide a more 'realistic' CV. The relative risk reduction (RRR) of PONV after propofol compared with inhalational agents is approximately 27% if N_2O is given with the inhalational agent.[46,48] Preliminary interviews suggested that respondents were not generally good at comprehending a relatively small difference in risk for PONV. This suggested that the willingness-to-pay values they gave would be lower than the full value of their preferred alternative. The scenarios were developed to reflect an intermediate position – that PONV was not prevented totally, but was reduced by double the reported RRR.

The descriptive scenarios were printed on coloured card and given before discharge to the adult patients, or parents or guardians, to take home. Patients were told they would be asked about these scenarios during the telephone interview at day 7 and were invited to give their preferences for, and valuations of, anaesthetics for day surgery. Individuals were asked clearly to state the additional value of their preferred option over the other option, in order to provide incremental monetary values. Although values were attached to the VAS, patients or parents or guardians were given the option of giving a valuation beyond the extremes of the range.

A question was directed to test patients' (or parents') understanding of the exercise, and thus the validity of the valuation given (see appendix 16).[241,242] Those values where understanding was not confirmed were excluded from analysis.

Costs

The cost per patient was estimated for each of the events listed in *Table 17* (resource use). The costs for each event (e.g. induction and maintenance of anaesthesia, adverse effect, PONV) were estimated for each patient in the trial. The costs were calculated as resource use multiplied by the unit cost of the specific resource.

TABLE 17 *Summary of the data requirements for the empirical study*

Data category	Parameters	Source (back-up source)
Demographic patient data	**Patient details**: name, hospital number, date of birth, sex, weight, telephone number, surgical procedure, ASA category, smoking status, GP	Patient notes (patient)
	Patient history: previous experience of anaesthetics, previous procedures	Day 7 telephone interview
Patient outcomes	**Clinical outcomes**: *Intraoperative events:* including adverse events	*In situ* data collection (patient notes, anaesthetic record)
	Postoperative events: time to recovery room discharge, PONV, pain, awareness, time to readiness for hospital discharge, overnight admission	*In situ* data collection (patient notes, nursing records)
	Postdischarge events: use of over-the-counter medication, readmission, GP contact	Day 7 telephone interview
	Patient preferences: CV	Day 7 telephone interview
Resource use	*Intraoperative*: induction and maintenance anaesthesia, other drugs, disposables, time in surgery, treatment of adverse events, staff time	*In situ* data collection (patient notes, anaesthetic record)
	Postoperative: PONV, pain, other drugs, other equipment, resource use associated with management of other adverse events, time to discharge, overnight admission, staff time	*In situ* data collection, discharge interview (patient notes, nursing records)
	Postdischarge: NHS contact	Day 7 telephone interview
Unit costs	*Variable resource use*: anaesthetic, drug and disposables costs, management of PONV and adverse events	Pharmacy and supplies department
	Staff resource use: standard costs for staff employed during pre- and postoperative assessment on the ward. Semi-fixed costs for running an anaesthetic room and operating theatre	Personnel and national salaries Finance department from one research site
	Fixed resource use: maintaining a ward, anaesthetic room, theatre and recovery area	

Table 17 provides a summary of the types of resource-use data collected at all stages of the empirical study. Resource use was divided into perioperative (anaesthetic room and theatre data) postoperative (recovery room and ward data) and postdischarge data.

Variable costs

Variable costs include items where the quantity of resources used is determined only by the need for them as inputs to individual patient care (see appendix 17).[243,244,245] Variable costs were primarily drugs and disposable equipment. Drug doses and routine events (e.g. use of a laryngeal mask) were recorded as they occurred, and the disposables and fluids associated with their administration were incorporated in the overall cost per dose. All disposables used during adverse events, including PONV, were recorded prospectively.

Inhalational agent resource use was recorded by the measurement of gas flow rates and by recording vaporiser settings at predefined intervals during the anaesthetic period. The Dion algebraic approximation was used to calculate the amount of volatile agent used.[24] A substudy was designed to assess the validity of the algebraic approximation used to estimate the quantity of volatile anaesthetic used by comparison with a weighing method (see appendix 18).[22,24,28,220,246,247]

Posthospital resource use was collected by a telephone interview with the patient or the patient's parent or guardian 7 days after discharge. If the patients were not contacted by telephone they were lost to follow-up.

Semi-fixed costs

Semi-fixed costs are those where the quantity of resources used is determined by organisational requirements as well as the need for them to provide care for individual patients (e.g. staff time). A substudy was designed to provide information on staff deployment and skill mix during the day-surgery episode. A semi-fixed resource use component was included for each arm of the study (see appendices 19[248,249] and 20[245,250,251]). Standard semi-fixed costs associated with staff resource use for admitting and discharging patients from the ward, transferring patients to and from theatre and monitoring patients postoperatively in recovery and on the ward were used in the baseline economic evaluation. Anaesthetic room and operating theatre semi-fixed costs were calculated using a different method. Average semi-fixed costs per minute were multiplied by the respective length of time patients spent in these areas for the adult and paediatric study, respectively.

Fixed costs

Fixed resource use associated with maintaining an anaesthetic room, operating theatre and ward for day-surgery procedures was included for each arm of the study (see appendix 21). The fixed cost per day-patient was estimated for three sections (ward, theatre, anaesthetic room) of the day-surgery episode.

Unit costs

Unit costs were obtained from the two NHS trusts in the study.

Data

A summary of the parameters investigated and the data collected prospectively in the CESA RCT is given in *Table 17*. A predefined quality control procedure was used to ensure consistency in data collection (see appendix 22).[252]

Data analysis

Clinical outcomes

PONV

The incidence of nausea, vomiting, and nausea and vomiting was analysed for each arm of the two studies. The incidence for the whole postoperative period was analysed. To assess whether any differences in PONV were due to the anaesthetic regimens or due to confounding factors such as age or gender, cross-tabulation and logistic regression were undertaken. Logistic regression was also used to adjust estimates of PONV risk, to allow for any residual effects of confounding variables arising from their not being exactly evenly distributed across the randomisation groups.

Adverse events

The incidence of individual adverse events, and the total incidence, was calculated for each arm of the study during the day-surgery episode. The total number and type of adverse events was recorded.

Patient preferences

The CVs collected were continuous variables. CVs that were categorised as invalid were excluded from the analysis. Descriptive summary statistics of the distribution of CVs were calculated.

Costs

The total cost was calculated for each of the patients enrolled in the trial and allocated to one of the comparators. The total cost was the sum of all costs incurred on behalf of the patient, from the perspective of the NHS. The variable costs and costs associated with postdischarge resource use were reported separately. The mean cost per patient for each comparator was estimated as the sum of the total costs for all patients randomised to that intervention, divided by the number of patients randomised. The costs incurred by the patient, from the perspective of the patient or parent/guardian, were reported separately.

The analysis excluded cost estimates for missing patients (patients who did not complete follow-up).

Incremental cost-effectiveness ratios

ICERs were calculated for the trial-based analyses and sensitivity analyses. The effectiveness measure for the calculation of the ICER was PONV (cost per case of PONV avoided). Variable costs were used in this analysis because the fixed costs component did not differ between randomisation arms. The interventions were ranked from highest to lowest cost. Interventions with high rankings on cost, which also have lower outcomes than the next most costly comparator, were treated as inefficient and excluded from further analysis. If the lowest cost intervention was also associated with better outcomes than more costly comparators, this was treated as efficient. Incremental ratios would not be calculated for this intervention, since its use would lead to both net savings and greater benefits than any other comparator.

ICERs were calculated for the remaining interventions. Each intervention was compared to the comparator ranked immediately below it in terms of cost. The incremental ratios were calculated as:

$$\text{ICER} = (\text{Cost A} - \text{Cost B})/(\text{Outcome A} - \text{Outcome B})$$

Statistical analyses

The SAS® and SPSS® statistical software packages were used. The objective of the statistical analysis was to test whether there were statistically significant differences between groups in the primary outcome (PONV), willingness-to-pay values, resource use and costs. Nominal data (e.g. incidence of PONV) were mainly analysed using the χ^2 test. So-called 'exact' tests were used when appropriate. Regression analyses were employed to confirm the findings from tabular analyses and to explore fine detail and interrelations not easily studied through tabulation.

Differences in mean values for continuous economic data were analysed using parametric tests of differences in mean values (length of stay, cost, CV and net benefit). Typically, these variables have positively skewed distributions.[253] The main options for statistical analysis were: standard non-parametric methods, data transformation, standard parametric methods, and non-parametric bootstrapping.

Arithmetic means provide a measure of central tendency that incorporates the full distribution of observations. The arithmetic mean is considered to be the most relevant measure for healthcare policy decisions, which should be based on information about the distribution of the costs of treating a patient group, as well as the average cost. The choice of statistical approach was based on the need to calculate and test for significant differences in the arithmetic mean in potentially skewed data.

Non-parametric statistical tests were considered inappropriate because they do not test differences in arithmetic means.[253] Similarly, data transformation to achieve approximate normality does not result in a comparison of arithmetic means (e.g. geometric means are derived during log transformation).

Bootstrapping compares arithmetic means, while avoiding distributional assumptions. This technique is most useful where the sample size is small to medium. Work carried out to compare the performance of bootstrapping with parametric *t*-tests has shown the *t*-test to be "remarkably robust to non-normality".[253] This robustness requires the sample size to be large enough for the central limit theorem to act sufficiently, or for the sample size and skewness to be similar in the groups under comparison.[254]

The *t*-test has been shown to be robust and give similar results to non-parametric bootstrapping with sample sizes of 148, where there was "severe non-normality".[253] The sample sizes in this study were much larger. It is suggested that in trials like this study, which are large enough to influence healthcare policy, standard *t*-test based approaches will be robust and give results very

similar to the bootstrap. Briggs and Gray[255] offer specific guidance for judging whether skew in the data will have important implications for the sampling distribution of the mean. They suggest that the skew in the sampling distribution of the mean (S_m) will be a factor: $S_m = S_S - \sqrt{n_S}$, where S_S is the skewness of the original sample and n_S is the number of observations in the original sample. When this rule was applied, the skewness in the samples was found to be sufficiently low to indicate normality for the sampling distribution of the mean.[255]

Therefore, the *t*-test was employed in this study. The *t*-test (and analysis of variance (ANOVA) for multiple group comparisons) was used for length of stay, cost, CV and net benefit variables.

Sensitivity analysis

Uncertainty: CESA RCT data

Sensitivity analysis was required to supplement the statistical analysis, in order to assess the level of uncertainty in the data collected within the CESA RCT and the subsequent internal robustness of the results. Sensitivity analysis was used to evaluate uncertainty for two cases, as described below.

Incremental cost-effectiveness ratios

Statistical analysis is not appropriate for testing the robustness of ICERs. It is not possible to generate 95% CIs around ICERs because the ratio of two distributions does not necessarily have a finite mean or, therefore, a finite variance.[256] The 95% CIs of the principal clinical outcome (PONV) were used to recalculate ICERs in order to assess the impact of uncertainty regarding clinical outcomes on ICERs. A simple deterministic sensitivity analysis was used to explore the impact of varying the incidence of PONV. The values for PONV incidence were varied between the limits of the 95% CIs. The low rate of PONV incidence for each arm was used simultaneously in the calculation of each ICER in the sensitivity analysis.

This was followed by the generation of a bootstrap estimate of the ICER sampling distribution to identify the magnitude of uncertainty around the ICERs. This method allowed uncertainty around both the costs and effects to be taken into account. Bootstrapping with replacement was employed, utilising Microsoft's Excel®, using 1000 iterations. The 2.5% and 97.5% percentiles of the ICER distribution were obtained.

Validity of the use of the Dion approximation of volatile consumption

A substudy showed that the Dion algebraic approximation consistently underestimated the amount of volatile anaesthetic used (see appendix 18). Results from this study suggested that the actual amounts of isoflurane and sevoflurane were 6% and 27% higher, respectively, than estimated. There was a wide variation in these inflation factors. One-way sensitivity analysis was used was to recalculate the variable costs using inflation factors. The total variable cost for each group was calculated for each inflation level. ICERs were recalculated for the range of inflation factors, if appropriate.

Uncertainty: differences between the CESA RCT and routine practice

The trial protocol and comparators were defined to reflect routine practice as far as possible. However, it was recognised that anaesthesia practice was changing. Additional analyses were planned to combine the CESA RCT data with published evidence to explore the relative costs and effects of anaesthesia practice not included in the trial. The literature review (see chapter 2) and the national survey (see chapter 3) indicated that some anaesthetic agents and practices now in use were not measured in the trial. Decision analysis and probabilistic sensitivity analysis were used to assess the impact of the following on patient outcomes and total costs:

- differences between the trial and routine practice in the use of prophylactic anti-emetics in adults (CESA MODEL)
- differences between the trial and routine practice in the inhalational anaesthetics used in children (CESA MODEL).

Additional data for these analyses were obtained from the literature review (see chapter 2) and national survey (see chapter 3). The literature review extracted and evaluated the clinical and economic evidence for the sensitivity analysis and modelling section. The data obtained from the survey are summarised in chapter 3.

The analysis of uncertainty used the mean costs and variance calculated for the trial-based analysis above. To extrapolate the results of the trial to alternative anaesthetic agents and PONV prophylaxis practices, the results of the trial were synthesised with the data from the literature reviews and national survey.

CESA models

Differences in the use of prophylactic anti-emetics

Approach

Decision analysis was used to estimate the expected costs, rates of PONV and ICERs if prophylactic anti-emetics were added to the anaesthetic regimen used in the CESA RCT (adults), or different anaesthetic agents were used for children. The structures of the decision trees (models) were validated, ensuring that the branch representing practice in the CESA RCT replicated the results of the trial.

Probabilistic sensitivity analysis was used to generate mean expected costs and outcomes and statistical measures of expected variance around the mean. This allows estimation of the probability and extent to which uncertainty and variation in the data used affect the absolute and relative costs and outcomes.[257] For this analysis each variable was assigned a base case or average value and a distribution of possible values. The probabilistic analysis summed the results of multiple analyses (iterations). Each iteration sampled the values for the variables at random from the specified distributions. The simulation package contained a component to determine the most appropriate distributional form to model the results of the empirical study. In some cases the package did not identify the distributional form that predicted the results of the empirical study. In these cases, a manual fit was obtained by identifying the distributional form that best predicted the empirical data available from the trial. Examples of the distributional forms that were explored are triangular, normal, truncated normal, uniform and beta subjective.

The sampling method used was Latin Hypercube, expected value. The simulation software used was @RISK,[258] as an add on to Microsoft Office Excel v. 7.0®. Every simulation requires sufficient iterations to ensure that each variable is sampled over the full distribution of values specified and that the statistics generated are reliable. As the number of iterations increases, the distribution of the outcomes is described in more detail and becomes more stable. The amount of change in the percentile values, mean and SD decreases with each subsequent iteration. The number of iterations for each simulation was determined by the software, which halted the simulation when convergence at less than 1.5% in percentile values, mean and SD was achieved. The simulation analyses gave estimates of the probability that the expected ICERs calculated could occur. The decision tree for the model was structured to mirror the trial. The literature review indicated that the likely sequence and structure of events was the same with and without anti-emetic prophylaxis (i.e. practice in the CESA RCT). What was expected to differ was the incidence and intensity of PONV, and the subsequent impact on costs.

The decision tree is presented in *Figure 1*. One branch emanating from the decision node of the tree represents the CESA RCT when a day patient was anaesthetised with one of the four anaesthetic agents (trial) and not given anti-emetic prophylaxis. The second branch of the decision model represents the scenario when a day patient was anaesthetised with one of the four anaesthetic agents and received a prophylactic 4 mg intravenous dose of ondansetron (model). Four decision trees, one for each anaesthetic regimen in the CESA RCT, were defined.

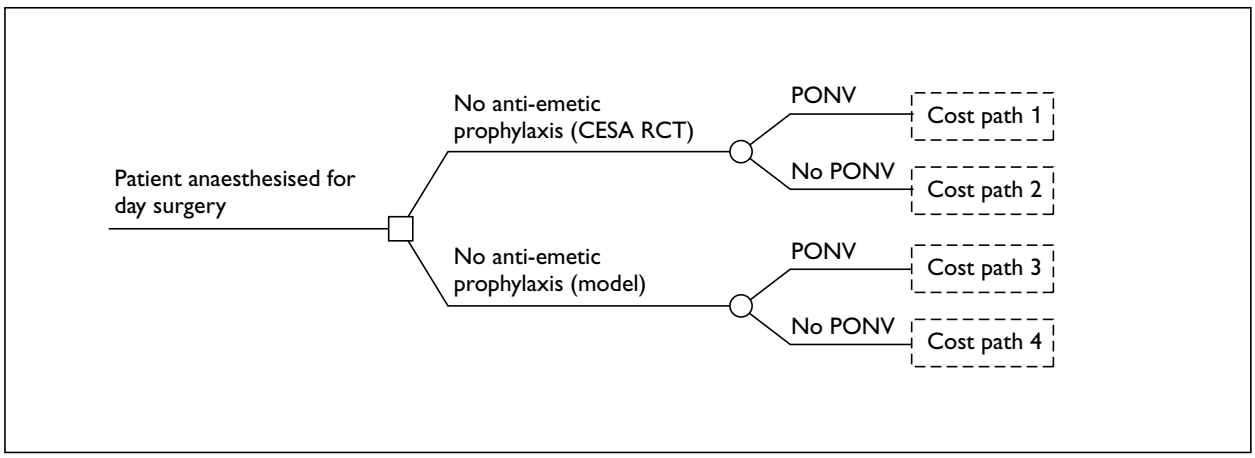

FIGURE 1 *The decision analytic model used to simulate the use of prophylactic anti-emetics*

Probability values

The proportion of the study population who received prophylactic ondansetron was derived from the results of the national survey and from the report by Simpson and Russell.[32] Therefore, 32% of the general patient study population, 41% of the orthopaedic study population and 61% of the gynaecological study population were assumed to have received a prophylactic anti-emetic (ondansetron).

The CESA RCT data on the incidence of PONV were used to estimate the average value and distribution of the probability of this event in the trial branch of the model. The triangular distribution (minimum, average, maximum value) was used for the simulation. The average was the observed incidence of PONV from the CESA RCT. The 95% CIs were used to determine minimum and maximum values for the distribution.

The probability of PONV with ondansetron was estimated from the observed incidence of PONV in the CESA RCT adjusted with the RRR for 4 mg intravenous ondansetron. The RRR was taken from a published meta-analysis (RRR 38.3%; 95% CI, 23.1 to 53.5) (see appendix 2).[48] The meta-analysis presented data for inpatient rather than day surgery. The baseline incidence of PONV without ondansetron in the meta-analysis was 40%, which was likely to be higher than the incidence of PONV for day surgery. However, this meta-analysis was used as the best estimate available for the effectiveness of ondanestron in managing PONV. A distribution was not fitted to the point estimate for relative risk used in the model.

Cost values

The mean variable costs of anaesthesia followed by PONV or no PONV were calculated from the CESA RCT.

The cost of intravenous ondansetron was calculated as £7.58 per patient (based on 4 mg per patient).[259]

The cost variables of the decision-analytic model were assigned the beta-subjective distribution (minimum value, mode, mean, maximum value), which makes limited assumptions regarding the shape of the distribution of the stochastic data from the empirical study.

Differences in the inhalational anaesthetics used in children

The impact of substituting isoflurane or sevoflurane into the propofol/halothane arm was investigated through simple modelling.

It was not satisfactory to assume that a quantity (in millilitres) of one anaesthetic was equivalent to another (i.e. 5 ml sevoflurane is not equivalent to administration of 5 ml halothane). To mirror actual practice as closely as possible, it was assumed that the clinical endpoint aimed for by administration of a volatile anaesthetic in the anaesthetic room or the operating theatre determined the quantity of volatile anaesthetic given. It was thus assumed that an equivalent MAC of anaesthetic would be given to achieve that clinical endpoint, irrespective of the particular anaesthetic given. MACs in oxygen for children were obtained from the product datasheets and were used to provide a standard measure of the dose of volatile agent administered. The MACs used for children were 1.08% for halothane,[260] 1.6% for isoflurane[260] and 2.4% for sevoflurane.[260] The following relationship was assumed:

$$\frac{\%\ \text{Concentration halothane administered}}{\text{MAC halothane}} = \frac{\%\ \text{Concentration [volatile}_2\text{] administered}}{\text{MAC [volatile}_2\text{]}}$$

where volatile$_2$ was either isoflurane or sevoflurane. This relationship was used to convert the percentage concentration of halothane administered to the percentage concentration of sevoflurane and the percentage concentration of isoflurane, at each time interval. The relative potentiation effect of N_2O and the differences in kinetics were ignored.

The new variable and total cost per patient were calculated. It was assumed there would be no impact on PONV because the literature review (see chapter 2) identified no difference in PONV between halothane and sevoflurane.

Net benefit

An exploratory analysis was carried out to assess the relative net benefit of the different anaesthetic agents. The CVs were combined with total costs per patient to derive a net benefit value for each patient. Net benefits were calculated for the CESA RCT analysis.

$$\text{Net benefit} = \text{Total cost} - \text{Total benefit}$$

$$= \text{Total cost} - (\text{CV[induction]} + \text{CV[maintenance]})$$

CVs were incorporated in the expression in the following way:

- Induction CVs were assigned a positive value (i.e. a negative cost) if the patient had received one mode of induction in the empirical study and then indicated that they would prefer that mode in the CV study.
- Maintenance CVs were assigned a positive value (i.e. a negative cost) if the patient had not experienced the adverse event of PONV.

Net benefit was calculated for each patient. To determine whether induction or maintenance CVs had the most significant effect on net benefit, net benefit was calculated using induction CVs only (Net[I]), using maintenance CVs only (Net[M]) and using both CVs (Net[I + M]).

A positive net benefit indicates the benefits from the intervention are worthwhile, while a negative net benefit indicates that the benefits are not value for money. For example, if the cost per case of PONV avoided was £1000, and decision-makers were willing to pay £1500 to avoid one case of PONV, the net benefit would £1000 – £1500 = £500. The results were presented as box and whisker plots (limits of the 5% and 95% percentiles) and cumulative percentages. It should be noted that health policy makers' and society's value of cases of PONV avoided were not generated by the data collected within the trial.

Chapter 5

Results of the adult economic evaluation

Recruitment to the CESA RCT

The study population was drawn from the patient population attending for selected elective day-surgery procedures, and who satisfied the inclusion and exclusion criteria.

During the recruitment period (October 1999 to January 2001), 1893 adults attending for the selected day-surgery procedures were screened, and 1548 adults were identified as eligible participants for the CESA RCT. The overall recruitment rate was 73% (1123/1548 patients identified as eligible). The reasons for non-participation are detailed in appendix 23. Ninety-five adults were withdrawn from the study after randomisation (see appendix 23). The remaining 1063 adult patients (265 propofol/propofol, 267 propofol/isoflurane, 280 propofol/sevoflurane, 251 sevoflurane/sevoflurane) remained in the study until discharge from hospital (see appendix 24). Fifteen per cent of these adult patients were then lost to follow-up 7 days after discharge. There was no difference in loss to follow-up between randomisation arms.

Numbers of patients

Table 18 summarises the number of adult patients in the study until hospital discharge, by individual study groups, and randomisation arms.

Patient characteristics

Table 19 summarises the age of the adult patients by study group. There were no differences between the randomisation arms in the average age of patients within each surgical group. *Table 20* gives age, ASA grade and surgical procedure by randomisation group. All 1063 patients were anaesthetised by physician anaesthetists. Within this, 33 consultant anaesthetists carried out 795 procedures

TABLE 18 *The number of patients in each arm of the adult study*

Procedure, gender	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
Total	265	267	280	251	1063
Gynaecology (St. Mary's)	28	25	25	25	103
Gynaecology (Wirral)	139	149	153	140	581
General, male	47	46	49	43	185
General, female	21	17	22	17	77
Orthopaedic, male	22	22	23	19	86
Orthopaedic, female	8	8	8	7	31

TABLE 19 *The age of patients in each group in the adult study*

Procedure, gender	No. of patients	Mean age (median, SD, range) (years)
Adult study	1063	44.1 (41.3, 15.1, 17.6–87.5)
Gynaecology (St. Mary's)	103	34.7 (33.4, 8.7, 17.6–59.6)
Gynaecology (Wirral)	581	41.7 (40.2, 12.2, 17.7–78.4)
General, male	185	55.2 (58.2, 18.3, 23.4–87.5)
General, female	77	49.9 (52.0, 17.4, 18.6–80.8)
Orthopaedic, male	86	41.1 (39.8, 14.7, 18.1–85.2)
Orthopaedic, female	31	46.9 (47.2, 14.8, 23.1–80.0)

TABLE 20 *Patient characteristics by anaesthetic regimen in the adult study*[*]

Parameter	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
No. of patients	265	267	280	251	1063
Mean age (median, SD, range) (years)	44.7 (41.0, 15.3, 18.1–80.8)	44.3 (42.1, 15.4, 17.6–86.6)	43.5 (41.3, 15.0, 17.7–83.6)	43.8 (40.4, 14.9, 19.0–87.5)	44.1 (41.3, 15.1, 17.6–87.5)
ASA grade I	182	182	187	169	720 (67.7%)
ASA grade II	76	78	83	72	309 (29.1%)
ASA grade III	2	0	6	3	11 (1.0%)
ASA grade not known	5	7	4	7	23 (2.2%)
Type of surgery					
Gynaecology, minor	72	81	81	71	305 (28.7%)
Gynaecology, intermediate	66	62	71	66	265 (24.9%)
Urology	44	45	45	38	172 (16.2%)
Knee	21	24	18	16	79 (7.4%)
Peritoneum	14	10	12	18	54 (5.1%)
Penis	15	8	13	10	46 (4.3%)
Vulva/vagina	7	13	6	6	32 (3.0%)
Tendons, muscles	5	7	6	7	25 (2.4%)
Peripheral, leg	5	3	8	5	21 (2.0%)
Skin, minor	3	5	6	2	16 (1.5%)
Bone	6	1	4	2	13 (1.2%)
Gastrointestinal, intermediate	4	2	2	2	10 (0.9%)
Joint	0	1	4	3	8 (0.8%)
Cervix	2	2	0	3	7 (0.7%)
Scrotum/testes	1	2	3	0	6 (0.6%)
Gastrointestinal, minor; breast; ear, minor	0	1	1	2	4 (0.4%)

[*] *See appendix 25*[261] *for surgical procedure categorisation and summary groups*

and 19 non-consultant anaesthetists carried out 268 procedures. The 1063 patients were treated by 34 surgeons of consultant and non-consultant grades.

Of the 1063 adult study participants, 156 (14.7%) were single, 751 (70.6%) were married, 116 (10.9%) were separated, 38 (3.6%) were widowed and two did not answer. Three-hundred and sixty-two (34.1%) adult study participants were current smokers and 271 (25.5%) were ex-smokers.

Employment details were recorded and categorised into social class for all male participants and for the male partners of female participants (employed and retired). In the case of single women, their own social class was recorded (see *Table 21*).

TABLE 21 *The social class of the participants in the adult study*

Social class	No. of patients	British value (%)[246]
I	50 (4%)	5
II	144 (13%)	16
IIIN	139 (13%)	35
IIIM	130 (12%)	19
IV	105 (9%)	18
V	16 (1%)	6
Unemployed, student, housewife	479 (45%)	Not given

Clinical outcome data

PONV by anaesthetic regimen

The incidence of PONV was analysed to assess whether the risk of PONV differed between the anaesthetic regimens. First, the crude (unadjusted) figures were tabulated. Further tables in appendix 26 display the association between PONV and other variables that plausibly might be associated with risk. Logistic regression analysis was employed to confirm the impression portrayed by the tabular analyses. It also adjusted the estimates of PONV risk to allow for any residual effects of the potential confounding variables that might arise from them not being exactly evenly distributed across the randomisation arms. The total numbers of subjects shown in the tables vary slightly, since some of the variables have missing data. Probability values presented with tables refer, unless otherwise stated, to a simple test for heterogeneity among categories. So-called 'exact' tests were employed when appropriate. Probability values are not presented for tables examining the distribution of potential confounding variables among the randomisation categories, as the statistical significance of observed differences is not relevant to the question of confounding.

Tables 22 and *23* give the occurrence of PONV, at varying degrees of severity, within the randomisation categories. For all PONV and for one or more episodes of vomiting a substantially larger proportion of cases occurred with the sevoflurane/sevoflurane regimen than with the others: 30% of the sevoflurane/sevoflurane category suffered PONV compared to 20% overall. Propofol/propofol appears to have the lowest (crude) incidence of PONV. Using this as the reference category the odds ratio (OR) for PONV in the sevoflurane/sevoflurane category is 2.7, suggesting a nearly three-fold risk of PONV. When one or more episodes of vomiting is considered the OR appears to be 6.14. However, this estimate is based on a small number of events, and is unreliable.

TABLE 22 *The occurrence of any PONV by anaesthetic regimen in the adult study*

	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
Total No. of patients	265 (100%)	267 (100%)	280 (100%)	251 (100%)	1063 (100%)
Nausea or vomiting – no	228 (86.0%)*	218 (81.6%)†	234 (83.6%)‡	176 (70.1%) *†‡	856 (80.5%)
Nausea or vomiting – yes	37 (14.0%)	49 (18.4%)	46 (16.4%)	75 (29.9%)	207 (19.5%)
OR§	1.00	1.38 (0.85–2.27)	1.24 (0.75–2.04)	2.69 (1.70–4.31)	–

* *Versus sevoflurane/sevoflurane*, p = *0.001; versus other arms, not significant*
† *Versus sevoflurane/sevoflurane*, p = *0.003; versus other arms, not significant*
‡ *Versus sevoflurane/sevoflurane*, p = *0.001; versus other arms, not significant*
§ *Calculated using propofol/propofol as reference*

TABLE 23 *The occurrence of one or more episodes of vomiting by anaesthetic regimen in the adult study*

	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
Total No. of patients	265 (100%)	267 (100%)	280 (100%)	251 (100%)	1063 (100%)
One or more episodes of vomiting – no	260 (98.1%)	253 (94.8%)	270 (96.4%)	225 (89.6%)	1008 (94.8%)
One or more episodes of vomiting – yes	5 (1.9%)	14 (5.2%)	10 (3.6%)	26 (10.4%)	55 (5.2%)
OR*	1.00	2.88 (0.96–10.34)	1.96 (0.60–7.41)	6.14 (2.26–20.75)	–

* *Calculated using propofol/propofol as reference*

The question of whether the relatively small differences in the risk of experiencing the other categories of PONV are compatible with chance effects was deferred until the logistic regression analysis. Two or more episodes of vomiting (*Table 24*) were so unusual that there are insufficient events for meaningful tabular analysis.

Table 25 displays the occurrence of PONV by randomisation group within each of the predefined study strata for randomisation. The small sizes of some of the strata lead to there being considerable random fog in the estimates of the risk of PONV. Nevertheless, the risk of PONV is markedly greatest in most of the strata under the sevoflurane/sevoflurane regimen.

Other adverse events

Table 26 summarises the degree-of-orientation categories of patients in recovery. Such differences as occur are small.

Other adverse events were recorded in the anaesthetic room, operating theatre, recovery room and ward. There was a low incidence of adverse events overall, and these are summarised in appendix 27. There was no difference between randomisation arms.

Previous anaesthetic experience

Patients reported a mean of 3.2 previous anaesthetic experiences (median 2.0, SD 3.8, range 0–41). There was no difference between randomised groups.

Logistic regression analysis of PONV

Logistic regression was employed using as the binary dependent variable either the presence/absence of any nausea or vomiting or the presence/absence of one or more episodes of vomiting. These analyses are not wholly independent of one another, but they serve to elucidate some of the fine detail of the patterns in the data and to adjust the estimates of the risks of PONV among the various anaesthetic regimens. The independent variables explored were anaesthetic regimen (categorical), age (numeric), gender (categorical), orientation (categorical), duration of anaesthesia (numeric), ASA grade (categorical), previous anaesthetics (numeric) and surgical procedure (categorical).

The analysis was performed in an exploratory manner (informed by the findings from the tables) rather than merely letting the analytic routine find the best-fitting, and not necessarily most informative, model. The final model selected (see below) turned out to be the best fitting, most parsimonious and intuitively most appealing among several candidate models.

The ASA grade and number of previous anaesthetics contributed nothing to the fit of the models and were discarded. The surgical procedure variable consisted of five groups (orthopaedic, male and female; general surgical, male and female; gynaecology) and thus contained information on gender and could not usefully be included in the regression model at the same time as gender. However, this variable was explored as an alternative to gender, but eventually discarded. A variant of the procedure categories pooled for the genders could be included in the model at the same time as gender, but contributed no explanatory power. It should be borne in mind that, as approximately half of the surgical procedures were for women only (gynaecology), and that as two-thirds of the adult patients were women, it is not surprising that this set of data offers only limited opportunities to explore the influence of gender and surgical procedure. No interaction terms, either between the anaesthetic regimen categories and the other variables, or between the other variables themselves, contributed anything useful to either the fit or the interpretation of the model.

TABLE 24 *The occurrence of two or more episodes of vomiting by anaesthetic regimen in the adult study*

	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
Total No. of patients	265 (100%)	267 (100%)	280 (100%)	251 (100%)	1063 (100%)
Two or more episodes of vomiting – no	264 (99.6%)	260 (97.4%)	274 (97.8%)	244 (97.2%)	1042 (98.0%)
Two or more episodes of vomiting – yes	1 (0.4%)	7 (2.6%)	6 (2.2%)	7 (2.8%)	21 (2.0%)
χ^2: p > *0.1*					

TABLE 25 *The occurrence of PONV by the strata within which random allocation to anaesthetic regimens was made in the adult study*

Stratum	Nausea or vomiting	Anaesthetic regimen				Total
		Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
General, female (Wirral)	None	18 (85.7%)	14 (82.4%)	19 (86.4%)	14 (82.4%)	65 (84.4%)
	Some	3 (14.3%)	3 (17.6%)	3 (13.6%)	3 (17.6%)	12 (15.6%)
	Total	21 (100.0%)	17 (100.0%)	22 (100.0%)	17 (100.0%)	77 (100.0%)
	OR*	1	1.29	0.95	1.29	–
General, male (Wirral)	None	45 (100.0%)	47 (100.0%)	48 (95.9%)	38 (90.5%)	177 (96.7%)
	Some	0 (0%)	0 (0%)	2 (4.1%)	4 (9.5%)	6 (3.3%)
	Total	45 (100.0%)	47 (100.0%)	50 (100.0%)	42 (100.0%)	184 (100.0%)
	OR†	–	–	1	2.53	–
Gynaecology (Wirral)	None	119 (82.6%)	109 (74.1%)	121 (79.6%)	88 (63.8%)	437 (75.2%)
	Some	25 (17.4%)	38 (25.9%)	31 (20.4%)	50 (36.2%)	144 (24.8%)
	Total	144 (100.0%)	147 (100.0%)	152 (100.0%)	138 (100.0%)	581 (100.0%)
	OR*	1	1.66	1.22	2.71	–
Gynaecology (St. Marys)	None	21 (75.0%)	19 (76.0%)	16 (64.0%)	13 (52.0%)	69 (67.0%)
	Some	7 (25.0%)	6 (24.0%)	9 (36.0%)	12 (48.0%)	34 (33.0%)
	Total	28 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	103 (100.0%)
	OR*	1	0.95	1.69	2.77	–
Orthopaedics, female (Wirral)	None	7 (87.5%)	6 (75.0%)	7 (87.5%)	4 (57.1%)	24 (77.4%)
	Some	1 (12.5%)	2 (25.0%)	1 (12.5%)	3 (42.9%)	7 (22.6%)
	Total	8 (100.0%)	8 (100.0%)	8 (100.0%)	7 (100.0%)	31 (100.0%)
	OR*	1	2.33	1.00	5.25	–
Orthopaedics, male (Wirral)	None	20 (95.2%)	25 (100.0%)	20 (100.0%)	16 (84.2%)	81 (95.3%)
	Some	1 (4.8%)	0 (0%)	0 (0%)	3 (15.8%)	4 (4.7%)
	Total	21 (100.0%)	25 (100.0%)	20 (100.0%)	19 (100.0%)	85 (100.0%)
	OR*	1	–	–	3.75	–

* *Reference regimen propofol/propofol;* † *Reference regimen propofol/sevoflurane*

TABLE 26 *The degree of orientation during recovery from anaesthesia in the adult study**

Degree of orientation	Anaesthetic regimen				Total
	Propofol/ propofol	Propofol/ isoflurane	Propofol/ sevoflurane	Sevoflurane/ sevoflurane	
Total	264 (100%)	267 (100%)	277 (100%)	246 (100%)	1054 (100%)
Alert	158 (59.8%)	158 (59.3%)	163 (58.8%)	140 (56.9%)	619 (58.8%)
Agitated and distressed	15 (5.7%)	21 (7.8%)	13 (4.7%)	19 (7.7%)	68 (6.4%)
Drowsy	91 (34.5%)	88 (32.8%)	101 (36.5%)	87 (35.4%)	367 (34.8%)

* *Nine missing values*

The findings from the logistic regression analyses are summarised in *Tables 27* and *28*. The ORs for age and duration of anaesthesia are displayed in two different ways to assist understanding. The adjusted ORs for the anaesthesia regimens are close to those shown in *Tables 23* and *24*. The risk of PONV or vomiting occurring is greatest for sevoflurane/sevoflurane, and this finding is extremely unlikely to be due to chance. Examination of the 95% CIs indicates that any differences between the other three regimens are compatible with chance effects. The findings for age, gender, orientation in recovery and duration of anaesthesia are consistent with those from the tabular analyses. None of these findings is surprising, given that the tabular analyses had

TABLE 27 *ORs from binary logistic regression for variables 'predicting' PONV in the adult study*

Predictor variable	OR (95% CI)
Age	
Age per 1-year increment	0.961 (0.946 to 0.976)
Age per 20-year increment	0.451 (0.329 to 0.615)
Duration of anaesthesia	
Duration of anaesthesia per minute	1.03 (1.02 to 1.04)
Duration of anaesthesia per 10 minutes	1.29 (1.16 to 1.44)
Anaesthetic regimen	
Propofol/propofol*	1
Propofol/isoflurane	1.29 (0.776 to 2.14)
Propofol/sevoflurane	1.22 (0.734 to 2.01)
Sevoflurane/sevoflurane	2.79 (1.73 to 4.51)
Orientation	
Alert*	1
Agitated and distressed	2.41 (1.34 to 4.32)
Drowsy	1.41 (0.983 to 2.02)
Gender	
Male*	1
Female	7.21 (3.64 to 14.3)

* *Reference category*

TABLE 28 *ORs from binary logistic regression for variables 'predicting' one or more episodes of postoperative vomiting in the adult study**

Predictor variable	OR (95% CI)
Age	
Age per 1-year increment	0.973 (0.949 to 0.998)
Age per 20-year increment	0.578 (0.351 to 0.961)
Duration of anaesthesia	
Duration of anaesthesia per minute	1.02 (1.01 to 1.04)
Duration of anaesthesia per 10 minutes	1.28 (1.09 to 1.50)
Anaesthetic regimen	
Propofol/propofol†	1
Propofol/isoflurane	2.73 (0.948 to 7.88)
Propofol/sevoflurane	2.04 (0.618 to 6.12)
Sevoflurane/sevoflurane	6.15 (2.30 to 16.5)
Gender	
Male†	1
Female	8.55 (2.04 to 35.8)

* *Note that orientation has been omitted as it had no explanatory power*
† *Reference category*

already established that the potential confounding variables are fairly evenly distributed among the anaesthesia regimen groups.

Resource use data

This section reports lengths of stay, total costs, variable costs, costs after hospital discharge and patients' own costs, by randomisation group. The length of stay and the principal cost parameters for the adult patients are summarised in *Table 29*.

Length of stay

The distribution of the data is shown in *Figure 2*. No statistically significant differences were found between the randomisation arms (ANOVA: F (3, 1059), 0.16; $p = 0.9229$).

The incidence of overnight admissions among the adult patients is summarised in *Table 30*. The most common reasons for overnight stays were more extensive surgery (16%), uncontrolled pain (15%), surgical complications (11%), social reasons (8%), PONV (8%), organisational reasons (5%) and prolonged effect of anaesthetic (5%).

More extensive surgery was particularly common in urology patients. When admissions for more extensive urological surgery were excluded, the overnight admissions rate was 7.4%.

Costs of patients

Total costs included all costs from the NHS perspective, including postdischarge costs (e.g. readmission, GP visits). Variable costs excluded staff, fixed and postdischarge costs. *Figures 3* and *4* present the data distribution of variable costs. No statistically significant differences in total costs were found between the randomisation arms (ANOVA: F (3, 1059), 1.41; $p = 0.2387$). Statistically significant differences in variable costs were found between randomisation arms (ANOVA: F (3, 1059), 95.24; $p = 0.0001$). Statistically significant differences were found between propofol/propofol and all other arms, and propofol/isoflurane and all other arms (Tukey's honestly significantly different (HSD) test, $p < 0.01$).

Postdischarge NHS costs and patients' own costs were obtained from 907 patients who were followed up with a telephone interview at day 7. Both cost parameters were minimal and did not differ between randomisation arms.

TABLE 29 *The length of stay and principal cost parameters in the adult study*

Parameter of interest	Anaesthetic regimen				Total (*n* = 1063)
	Propofol/ propofol (*n* = 265)	Propofol/ isoflurane (*n* = 267)	Propofol/ sevoflurane (*n* = 280)	Sevoflurane/ sevoflurane (*n* = 251)	
Mean (SD) length of stay (h)	8.9 (10.9)	9.3 (11.4)	8.8 (10.9)	9.3 (11.8)	9.1 (11.2)
Mean (SD) total cost (£)	131.7 (80.0)	118.7 (85.1)	123.4 (83.9)	131.3 (95.9)	126.1 (86.3)
Mean (SD) variable cost (£)	21.1 (12.2)	7.1 (4.4)	13.8 (11.7)	15.3 (6.8)	14.4 (10.6)
Patients' own costs (SD) (£)	0.12 (0.41) (*n* = 228)	0.10 (0.41) (*n* = 232)	0.08 (0.32) (*n* = 235)	0.13 (0.51) (*n* = 212)	0.11 (0.41) (*n* = 907)
Postdischarge NHS costs (SD) (£)	3.3 (10.3) (*n* = 228)	4.0 (17.1) (*n* = 232)	6.1 (23.9) (*n* = 235)	6.3 (44.5) (*n* = 212)	4.9 (26.8) (*n* = 907)

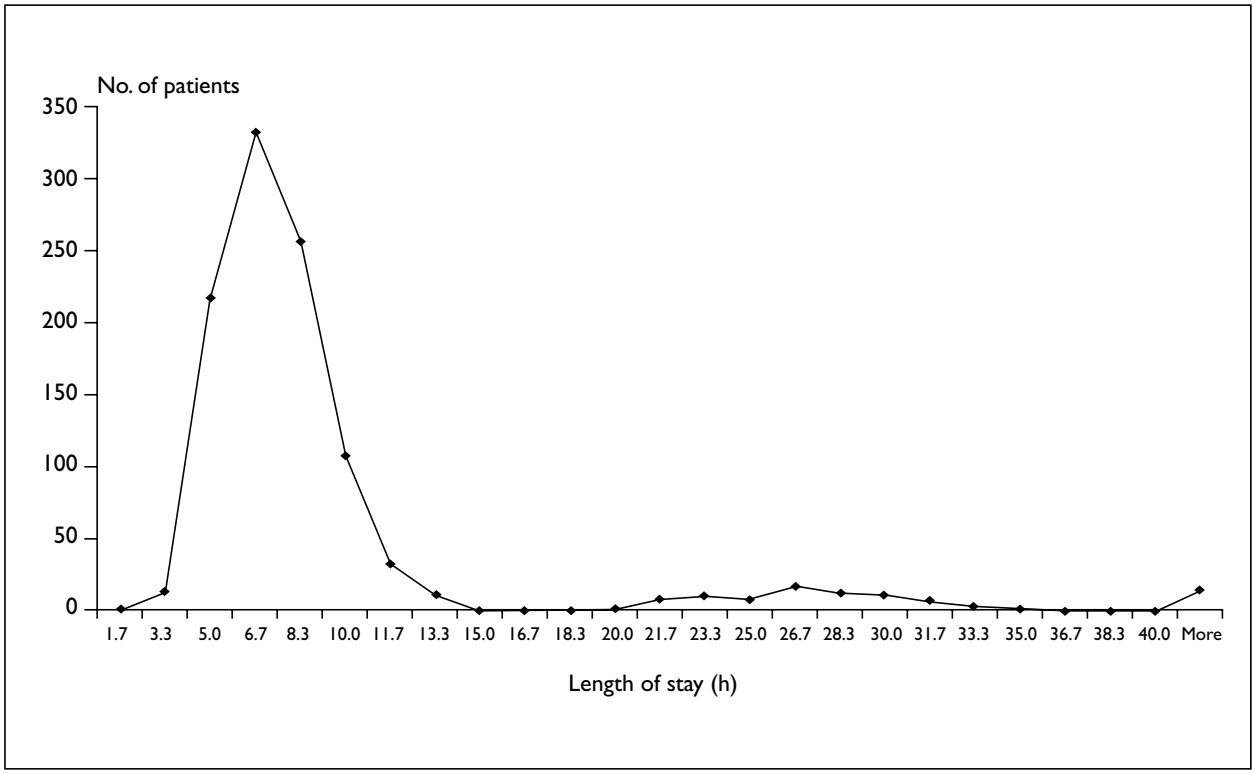

FIGURE 2 *The length of stay of patients in the adult study*

Patient preference and CV data

Preference for induction of anaesthesia

In total, 907 patients were available for interview and were asked to express a preference for scenario A (intravenous anaesthetic) or scenario B (inhalation anaesthetic) (*Table 31*). The results show that 79% patients who had received intravenous induction would prefer that method in the future to inhalational induction. The majority of patients who had received inhalational induction (64%) would prefer that method in the future to intravenous induction. This suggests that patients would prefer the method of induction with which they feel more familiar, although 68% patients who were followed up favoured the intravenous method overall.

CVs for induction of anaesthesia

Patients were asked to give a value for their expressed preference. Patients who gave valuations that were classed as invalid (see appendix 16) were excluded from the analysis. A minority of patients, who gave responses of 'more than £250' but did not give an actual value were also excluded. A total of 773 responses were used in the analysis. The

TABLE 30 *Overnight admissions in the adult study*

Procedure, gender	No. of patients in surgical group	No. of overnight stays (% of group)
Adult study	1063	94 (8.8%)
Gynaecology (St. Mary's)	103	14 (13.6%)
Gynaecology (Wirral)	581	29 (5.0%)
General, male	185	33 (17.8%)
General, female	77	10 (13.0%)
Orthopaedic, male	86	5 (5.8%)
Orthopaedic, female	31	3 (9.7%)

CVs given by adults for induction, by randomisation group, are summarised in *Table 32*. The mean CVs were higher for intravenous induction than for inhalational induction for all randomisation arms, indicating a higher magnitude of preference for intravenous induction among those who preferred it. Those patients who had received inhalational induction, but wanted intravenous induction next time, exhibited smaller CV values than those who had received intravenous induction.

The CVs for induction were compared between those patients who received propofol induction and those who received sevoflurane induction. Where intravenous induction was the preferred option, those patients who received propofol induction in the study did not give significantly higher CVs than those who received sevoflurane induction ($p = 0.10$). Where inhalational induction was the preferred option, those patients who received propofol induction in the study did not give significantly different CVs than those who received sevoflurane induction, although there was a tendency for the CVs to be lower ($p = 0.085$).

Figure 5 shows the distribution of CVs for induction. It is clear that there is a scale effect for scenario A (intravenous), but not for scenario B (inhalational), which was not evident in the piloting work. Many patients' responses appear to have been constrained by the scale (£0 to £250), despite pilot work and the option to provide a value beyond the limits of the scale. This suggests that the more recent the experience of anaesthesia, the stronger the preferences expressed. It also suggests that the CVs reported here are conservative rather than extravagant values.

Patient preferences for maintenance of anaesthesia

A total of 907 patients were asked for a preference for a reduced risk of PONV (scenario C, PONV risk 7/10; scenario D, PONV risk 3/10) (*Table 33*). The results show that 97% patients would choose the scenario where the risk of PONV was reduced. The patients who picked scenario C were con-

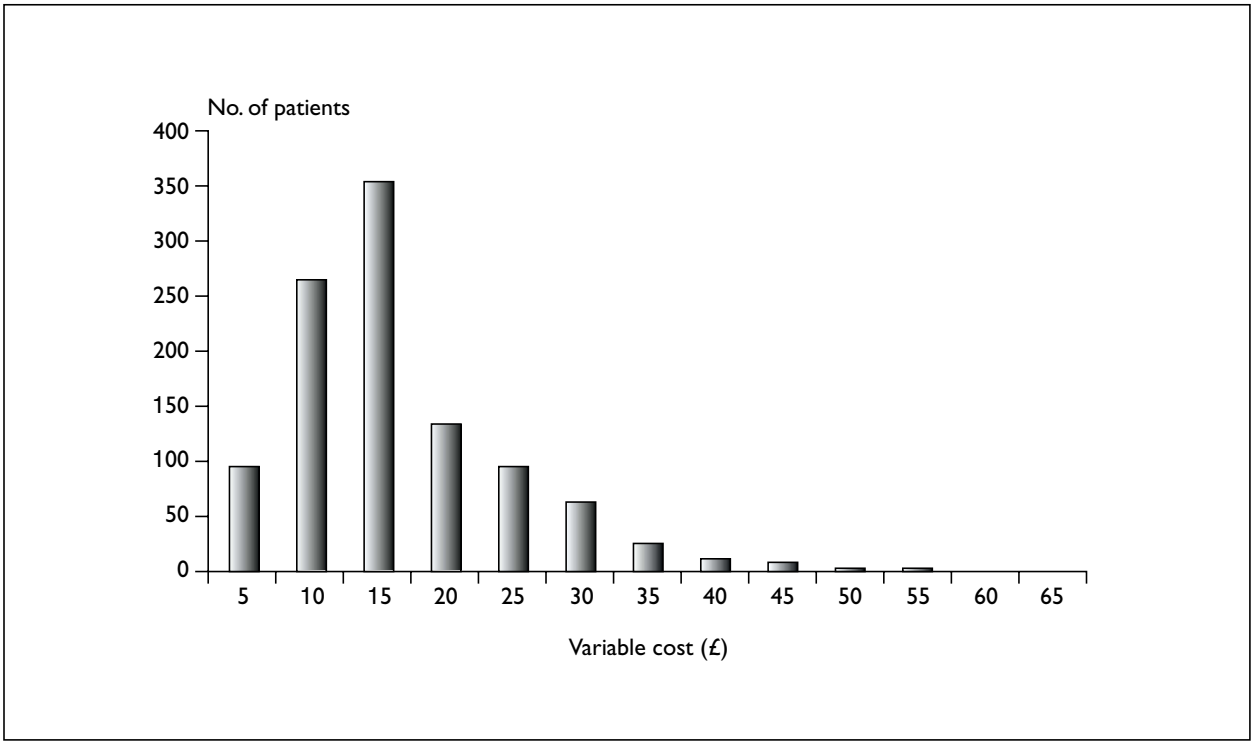

FIGURE 3 *Distribution of the variable costs of patients in the adult study*

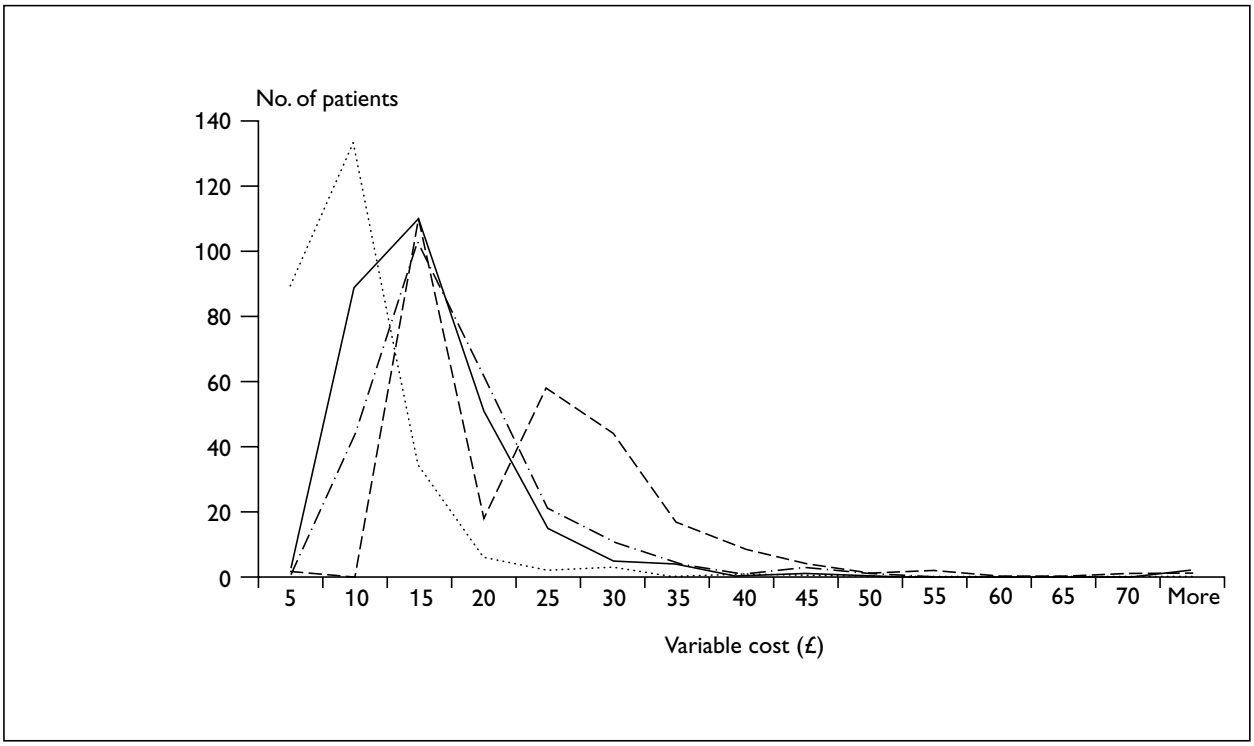

FIGURE 4 *Distribution of the variable costs of patients by anaesthetic regimen in the adult study (– – –, propofol/propofol; ·····, propofol/isoflurane; ——, propofol/sevoflurane; – · – ·, sevoflurane/sevoflurane)*

TABLE 31 *Incidence of preference for intravenous anaesthetic (scenario A) or inhalational anaesthetic (scenario B), by anaesthetic regimen in the adult study*

Anaesthetic regimen	Total No. of patients	Preference for A	Preference for B	No preference	Not answered	Lost to follow-up
Adult study	1063	615	275	16	1	156
Propofol/propofol	265	173	52	3	0	–
Propofol/isoflurane	267	190	41	1	0	–
Propofol/sevoflurane	280	186	47	2	0	–
Sevoflurane/sevoflurane	251	66	135	10	1	–

TABLE 32 *CVs for induction with intravenous anaesthetic (scenario A) or inhalational anaesthetic (scenario B), by anaesthetic regimen in the adult study (invalid answers excluded)*

Anaesthetic regimen	No. who chose A	Mean (SD) CV for A (£)	No. who chose B	Mean (SD) CV for B (£)
Total No. of patients	534	236.9* (370)	239	143.5* (110)
Propofol/propofol	153	232.2 (286)	40	153.1 (115)
Propofol/isoflurane	167	280.9 (570)	39	104.5 (79)
Propofol/sevoflurane	162	210.3 (181)	40	136.9 (106.4)
Sevoflurane/sevoflurane	54	193.5 (156)	120	155.2 (116)

* $p = 0.0001$

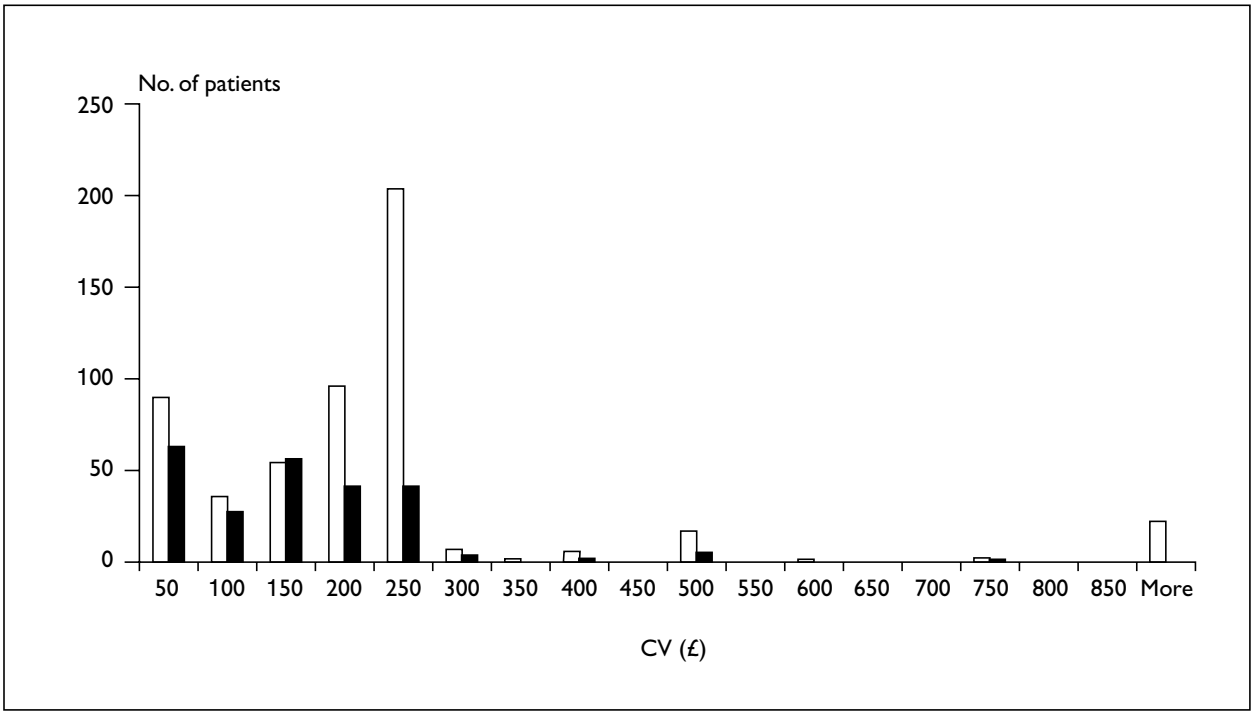

FIGURE 5 *Distribution of the CVs for induction with intravenous anaesthetic (scenario A) or inhalational anaesthetic (scenario B) in the adult study (□, scenario A; ■, scenario B)*

TABLE 33 *The incidence of preference for a PONV risk of 7/10 (scenario C) or 3/10 (scenario D), by anaesthetic regimen in the adult study*

Anaesthetic regimen	Total No. of patients	Preference for C	Preference for D	No preference	Not answered	Lost to follow-up
Adult study	1063	28	854	22	3	156
Propofol/propofol	265	9	214	3	2	–
Propofol/isoflurane	267	5	221	6	0	–
Propofol/sevoflurane	280	9	220	6	0	–
Sevoflurane/sevoflurane	251	5	199	6	2	–

sidered to have given invalid responses. These responses were excluded from the analysis.

CVs for maintenance of anaesthesia

Patients were asked to give a value for their expressed preference. Patients who gave valuations that were classed as invalid (see appendix 16) were excluded from the analysis. A minority of patients who gave responses of 'more than £250' but did not give an actual value were also excluded. A total of 788 responses were used in this analysis. *Table 34* summarises the CVs given by adults for maintenance, by randomisation group. The mean CVs for avoidance of PONV tended to

TABLE 34 *CVs for maintenance anaesthesia with a PONV risk of 7/10 (scenario C) or 3/10 (scenario D), by anaesthetic regimen in the adult study (invalid answers excluded)*

Anaesthetic regimen	No. who chose C	No. who chose D	Mean (SD) CV for D (£)	Mean (SD) x 2.5 for D (£)
Adult study	26	788	191.7 (149)	479.2 (372.4)
Propofol/propofol	8	194	202.5 (191)	506.3 (477.4)
Propofol/isoflurane	5	204	192.3 (128)	480.6 (321.2)
Propofol/sevoflurane	5	205	196.1 (151)	480.2 (376.7)
Sevoflurane/sevoflurane	8	185	174.8 (113)	437.0 (283.5)

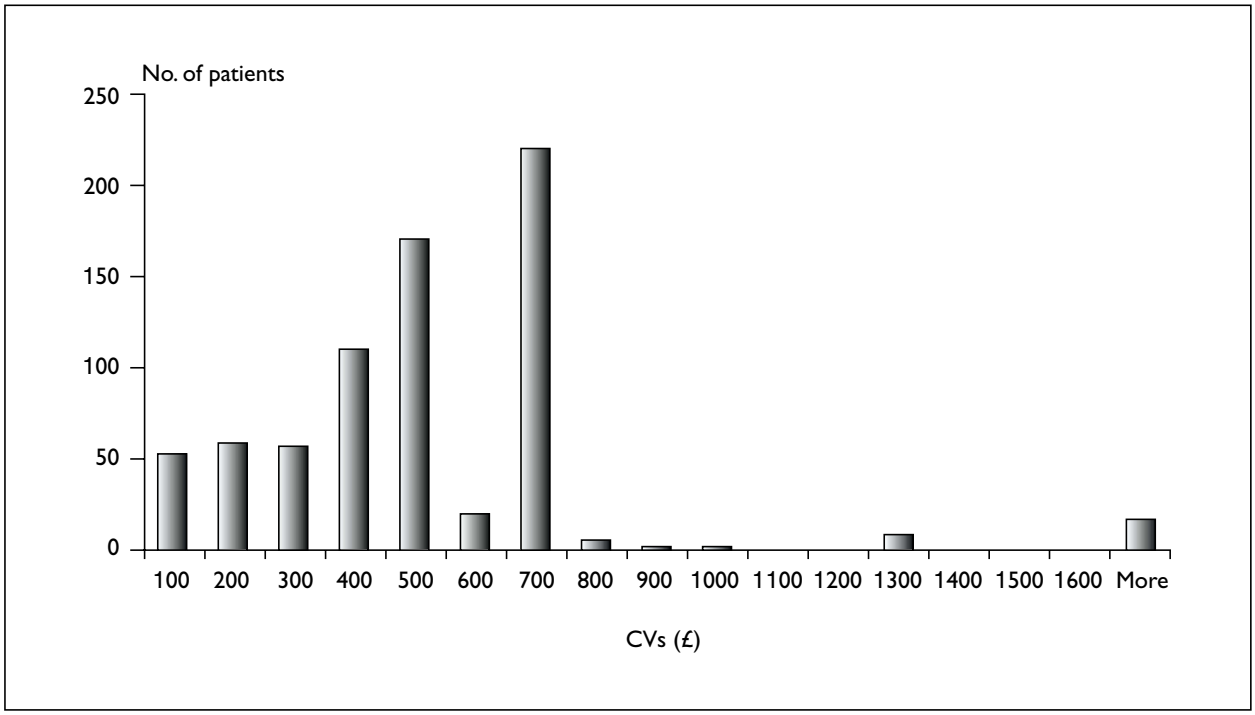

FIGURE 6 *Distribution of CVs for avoidance of PONV after maintenance anaesthesia (scenario D) in the adult study*

be lower in the sevoflurane/sevoflurane group than for the other randomisation arms, although this did not reach statistical significance. This indicated a tendency to a lower magnitude of preference for PONV avoidance in the group with a significantly higher risk of PONV (versus propofol/propofol, $p = 0.098$; versus propofol/volatile arms, $p = 0.093$). The CVs given by patients who received the propofol/propofol regimen were no different from those given by the patients who had received the combination of intravenous and inhalational anaesthesia ($p = 0.589$).

The mean CVs for those patients who had and who did not have PONV were £199.8 ($n = 135$, SD = £142.0) and £192.6 ($n = 574$, SD = £156.8), respectively ($p = 0.565$). Therefore, the CV of patients was not affected by their experience of the clinical outcome. This conclusion was not altered when CVs were corrected by a factor of 2.5. *Figure 6* shows the distribution of CVs for maintenance anaesthesia. It is clear that there is been a scale effect for scenario D.

Reported income bands

Table 35 summarises the reported monthly income bands of the adult study participants. There was no difference in distribution between the randomisation arms.

Income was not correlated with CVs (induction CVs, Spearman's $\rho = -0.126$, $p = 0.0009$; maintenance CVs, Spearman's $\rho = -0.074$, $p = 0.057$) (*Figures 7* and *8*).

TABLE 35 *Reported monthly household income bands of participants in the adult study*

Monthly household income	No. of patients
> £2000	148 (13.9%)
£1001 to £2000	304 (28.6%)
£501 to £1000	235 (22.1%)
£250 to £500	150 (14.1%)
< £250	23 (2.2%)
Income not given	44 (4.1%)
Lost to follow-up	159 (15.0%)

Incremental cost-effectiveness ratios

Sevoflurane/sevoflurane was less effective and more costly than either of the mixed anaesthesia regimens (i.e. was dominated by them). It was less effective, but less costly than the propofol/propofol regimen, giving an ICER of £46.1 per PONV episode avoided for this comparison.

Table 36 summarises the ICERs for propofol/propofol and propofol/sevoflurane when they are each compared to the least costly and least effective (propofol/isoflurane) regimen.

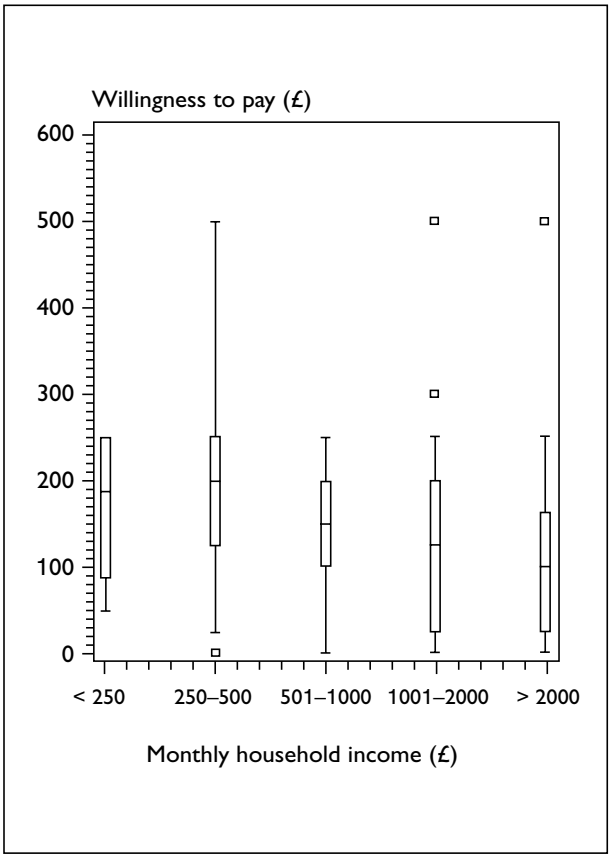

FIGURE 7 *Willingness to pay for induction anaesthesia versus monthly household income (limit 5% and 95% percentiles) in the adult study*

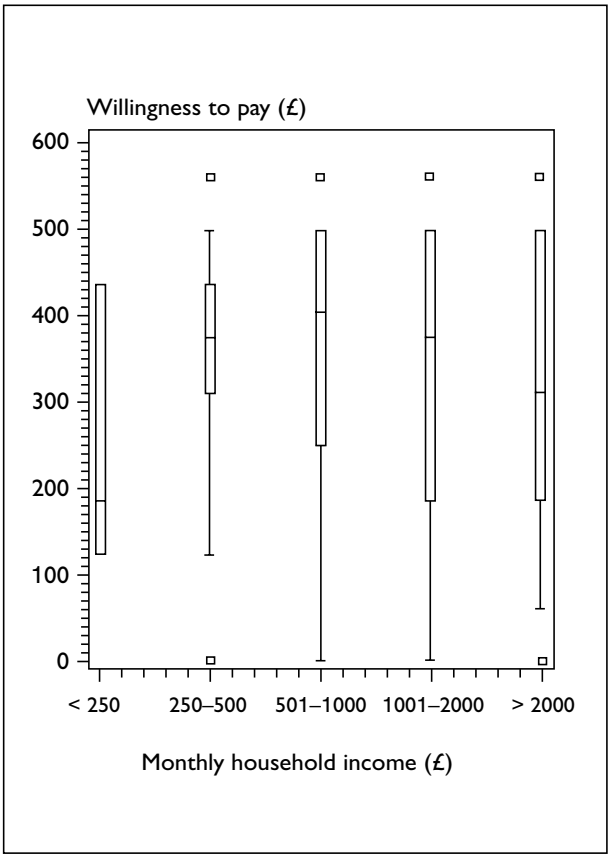

FIGURE 8 *Willingness to pay for maintenance anaesthesia versus monthly household income (limit 5% and 95% percentiles) in the adult study*

TABLE 36 *ICERs with respect to propofol/isoflurane in the adult study*

Anaesthetic regimen	Total variable cost for the group (mean cost per patient) (£)	No. of patients with PONV	ICER per PONV instance avoided (£)
Propofol/propofol	5591.5 (21.1)	37 (14.0%)	296
Propofol/sevoflurane	3864.0 (13.8)	46 (16.4%)	333
Propofol/isoflurane	1975.8 (7.4)	49 (18.4%)	–
Sevoflurane/sevoflurane	3840.3 (15.3)	75 (29.9%)	Dominated

Sevoflurane/sevoflurane was dominated. As the cost increases, so does effectiveness, although it must be noted that these differences in effectiveness are not statistically significant.

No statistically significant differences were found in the rate of PONV between propofol/propofol, propofol/sevoflurane and propofol/isoflurane. If this is because the regimens were equivalent, then the least costly of these alternatives is likely to be the most cost-effective. In this analysis, that would be propofol induction followed by isoflurane maintenance anaesthesia.

Sensitivity analysis

Uncertainty: CESA RCT data

Incremental cost-effectiveness ratios

Table 37 shows the results of a deterministic sensitivity analysis on the observed rate of PONV. The modelled baseline values for the ICERs closely match the values from the empirical study. The two sets of values do not match exactly due to arithmetic rounding. This sensitivity analysis shows that the rank order of the ICERS is robust in terms of the observed rate of PONV. However, given that the low rate of PONV for each arm was used

TABLE 37 *Deterministic sensitivity analysis on the rate of PONV in the adult study*

Parameter of interest	Anaesthetic regimen			
	Propofol/ propofol (*n* = 265)	**Propofol/ isoflurane (*n* = 267)**	**Propofol/ sevoflurane (*n* = 280)**	**Sevoflurane/ sevoflurane (*n* = 251)**
Mean cost per patient with PONV (£)	21.55	9.60	16.34	18.21
Mean cost per patient with no PONV (£)	21.07	6.91	13.24	14.10
Probability of PONV (low and high values)	0.14 (low 0.10; high 0.18)	0.18 (low 0.13; high 0.23)	0.17 (low 0.13; high 0.21)	0.30 (low 0.24; high 0.36)
Probability of no PONV (= 1 – probability of PONV)	0.86	0.82	0.83	0.70
Expected variable cost per patient (low and high values) (£)	21.14 (low 21.12; high 21.16)	7.39 (low 7.26; high 7.53)	13.77 (low 13.64; high 13.89)	15.33 (low 15.09; high 15.58)
Incidence of PONV from empirical study	37 (14.0%)	49 (18.4%)	46 (16.4%)	75 (29.9%)
Baseline ICER (best and worse cases) (£/PONV case avoided)	307* (best case 374; worst case 242)	–	319† (best case 638; worst case 318)	Dominated

* *Calculated with respect to the propofol/sevoflurane regimen*
† *Calculated with respect to the propofol/isoflurane regimen*

simultaneously this is not surprising. The bootstrapping approach reported in the next section further explored the volatility in the rank ordering of the ICERs.

Bootstrapped distributions of ICERs

Bootstrapped distributions of ICERs were generated for all combinations, excluding sevoflurane/sevoflurane (*Figures 9* to *11*). The cost-effectiveness planes generated for propofol/propofol versus propofol/isoflurane (2.5% percentile, –£2683; 97.5% percentile, £1904) and versus propofol/sevoflurane (2.5% percentile, –£6878; 97.5% percentile, £2192) and for propofol/sevoflurane versus propofol/isoflurane (2.5% percentile, –£11441; 97.5% percentile, £1844) confirm that the rank order of these ICERs is not robust.

Validity of the use of the Dion approximation of volatile consumption

A substudy showed that the Dion algebraic approximation consistently underestimated the amount of volatile anaesthetic used (see appendix 18). Results from this study suggested that the actual amounts of isoflurane and sevoflurane were between 6% and 27% higher than estimated. The variable costs were therefore recalculated using these inflation factors (*Table 38*).

It can be seen that the arms most affected are those containing sevoflurane, due to the high relative acquisition cost of this agent. However, the rank order of the alternatives does not change, and so the conclusions regarding cost-effectiveness do not change from those for the base case.

Uncertainty: differences between the CESA RCT and routine practice

Simulation of the use of prophylactic anti-emetics

The cost variables of the decision-analytic model were assigned the beta-subjective distribution (minimum value, mode, mean, maximum value), which makes limited assumptions regarding the shape of the distribution of the stochastic data from the empirical study. *Table 39* reports the distributions and RRRs for the simulation.

Figures 12 to *15* show the completed decision trees for the simulation. The branch of the tree for no anti-emetic prophylaxis models the results of the empirical study accurately. The mean and standard deviation of the simulation (*Table 40*) mirror the empirical study results (see *Table 29*).

Table 41 shows the expected costs and predicted outcome (with the 95% CIs) for the study

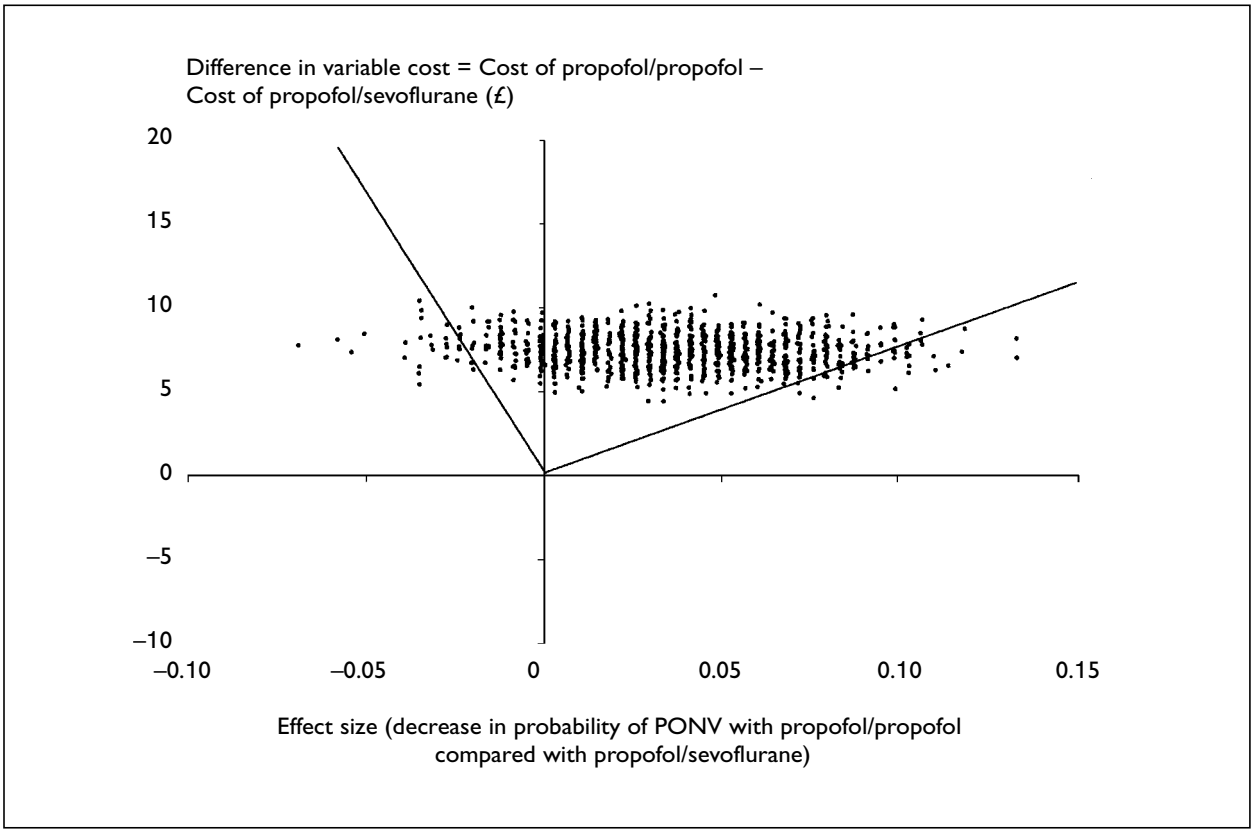

FIGURE 9 *The cost-effectiveness plane for propofol/propofol versus propofol/sevoflurane (the 2.5% and 97.5% percentile boundaries are indicated by the straight line from the origin) in the adult study*

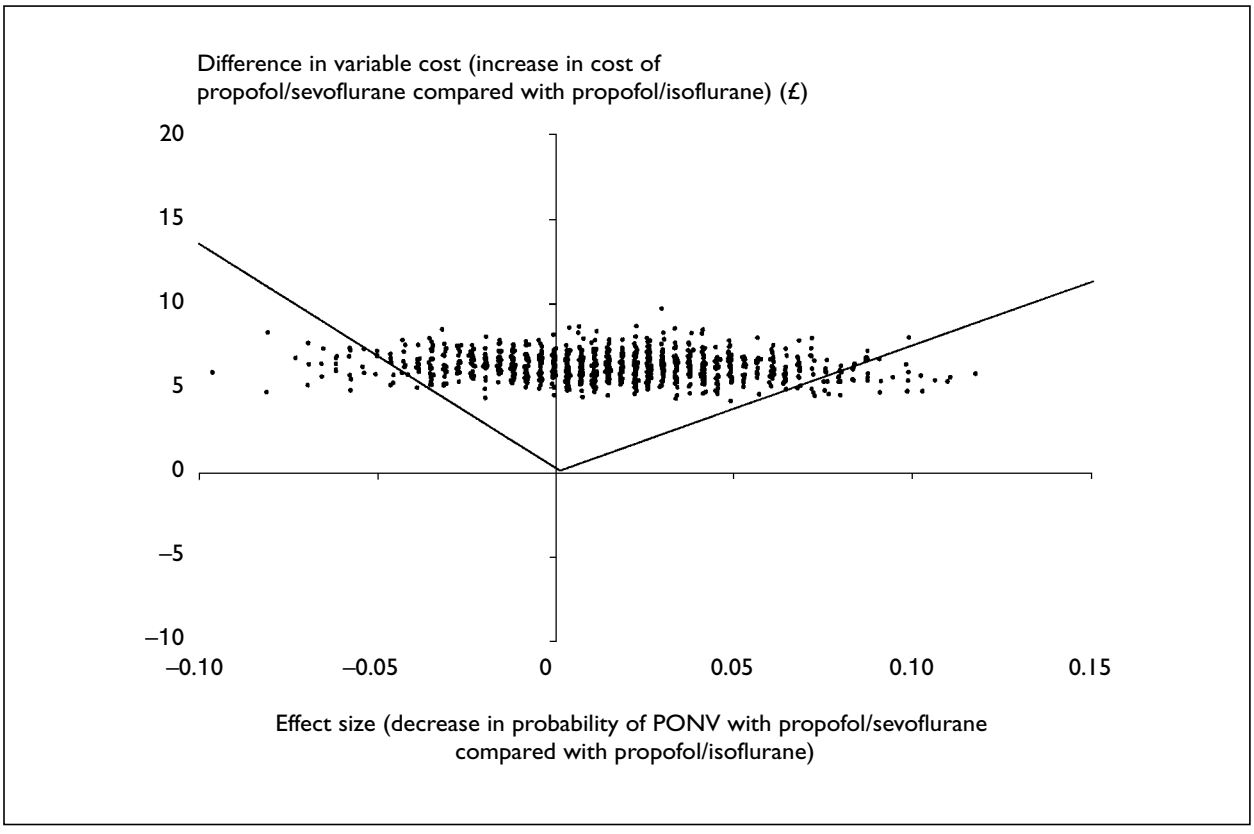

FIGURE 10 *The cost-effectiveness plane for propofol/sevoflurane versus propofol/isoflurane (the 2.5% and 97.5% percentile boundaries are indicated by the straight line from the origin) in the adult study*

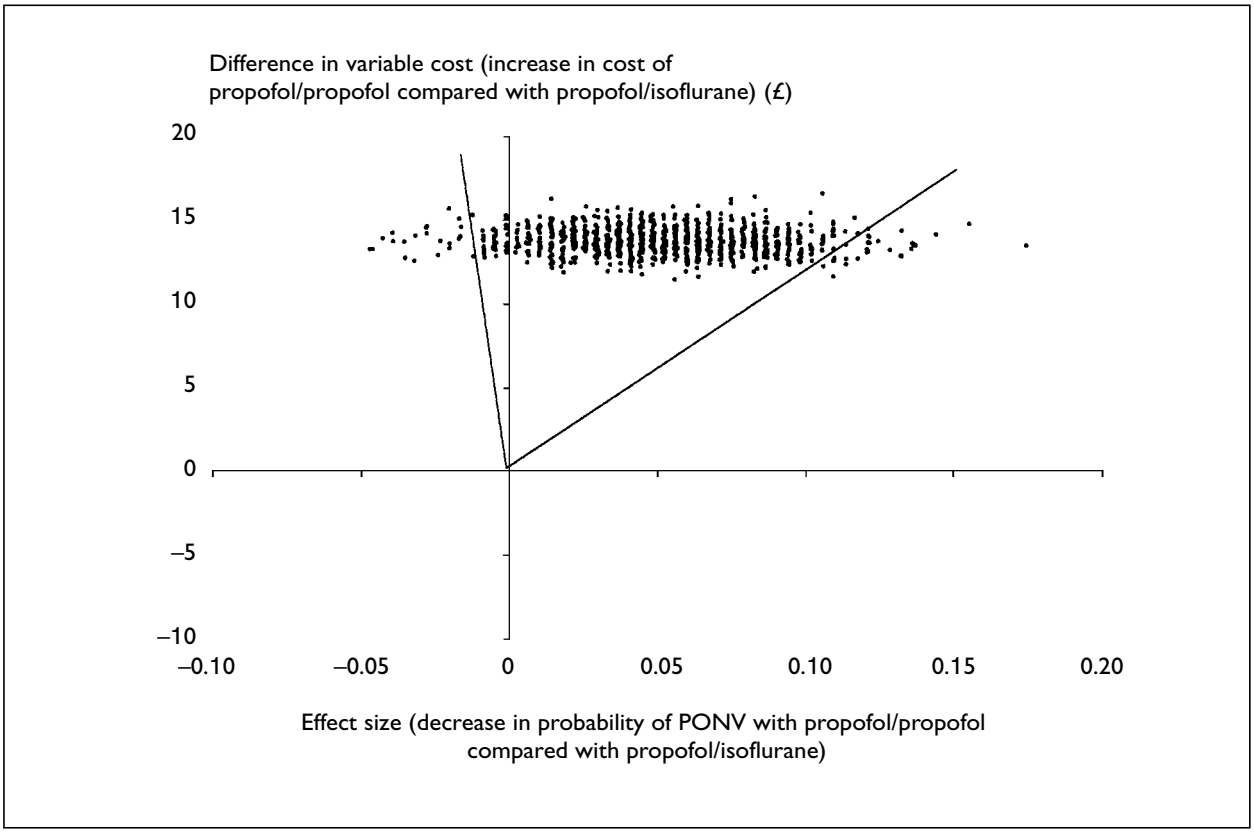

FIGURE 11 *The cost-effectiveness plane for propofol/propofol versus propofol/isoflurane (the 2.5% and 97.5% percentile boundaries are indicated by the straight line from the origin) in the adult study*

TABLE 38 *The impact of inflation of the costs of anaesthetic agents on the variable costs in the adult study*

Parameter of interest	Mean (SD) variable cost (£)			
	Propofol/ propofol (*n* = 265)	Propofol/ isoflurane (*n* = 267)	Propofol/ sevoflurane (*n* = 280)	Sevoflurane/ sevoflurane (*n* = 251)
Base case	21.1 (12.2)	7.1 (4.4)	11.4 (11.4)	13.8 (11.7)
Inflation correction	21.1 (12.2)	7.6 (4.4)	14.5 (11.8)	16.3 (7.1)

population if they were to receive ondansetron. In the simulation the most effective and costly arm was propofol/propofol. The ICERs derived with respect to the next highest ranked in terms of effectiveness are summarised in *Table 41*.

The main stated advantage of TIVA is that it reduces the need for prophylactic anti-emetics. *Table 42* shows the results of the simulation where all study groups except propofol/propofol (TIVA) receive prophylactic ondansetron. The costs and outcomes for TIVA from the empirical study are also included in this table. In this simulation propofol/propofol is dominated by propofol/sevoflurane. The ICERs derived with respect to the next highest ranked in terms of effectiveness are summarised in *Table 42*.

Net benefit

Net benefit was only calculated in those patients who had given a valid CV for both scenarios (n = 709). *Table 43* summarises net benefit by randomisation for:

- mean net benefit (induction only, Net[I])
- mean net benefit (maintenance only, Net[M])
- mean net benefit (induction and maintenance, Net[I + M]).

A positive net benefit is equivalent to a negative net cost. Statistically significant differences were found between the study

TABLE 39 *RRRs for PONV in the adult study*

Variable	Assigned distribution*			
	Propofol/ propofol	**Propofol/ isoflurane**	**Propofol/ sevoflurane**	**Sevoflurane/ sevoflurane**
Probability of PONV with no ondansetron (path 1)	0.14 Triangular: 0.10–0.18	0.18 Triangular: 0.13–0.23	0.17 Triangular: 0.13–0.21	0.30 Triangular: 0.24–0.23
Probability of PONV with ondansetron (path 3)	0.05 Triangular: 0.03–0.07	0.07 Triangular: 0.04–0.10	0.07 Triangular: 0.04–0.09	0.11 Triangular: 0.07–0.16
Mean cost of PONV with no ondansetron (path 1)	21.55† Beta subjective: 10.8, 10.9, 21.55, 51.16	9.60 Beta subjective: 3.8, 3.9, 9.60, 17.61	16.34 Beta subjective: 7.4, 7.4, 16.34, 33.78	18.21 Beta subjective: 7.1, 7.2, 18.21, 45.84
Mean cost of no PONV with no ondansetron (path 2)	21.07 Beta subjective: 2.3, 10.9, 21.07, 147.69	6.91 Beta subjective: 1.2, 1.3, 6.91, 38.76	13.24 Beta subjective: 3.7, 3.8, 13.24, 135.91	14.10 Beta subjective: 4.7, 4.8, 14.10, 44.47
Mean cost of PONV with ondansetron (path 3)	25.44 Beta subjective: 10.8, 10.9, 21.55, 51.16	13.52 Beta subjective: 3.8, 3.9, 9.60, 17.61	20.27 Beta subjective: 7.4, 7.4, 16.34, 33.78	22.17 Beta subjective: 7.1, 7.2, 18.21,45.84
Mean cost of no PONV with ondansetron (path 4)	24.96 Beta subjective: 2.3, 10.9, 21.07, 147.69	10.83 Beta subjective: 1.2, 1.3, 6.91, 38.76	17.17 Beta subjective: 3.7, 3.8, 13.24, 135.91	18.06 Beta subjective: 4.7, 4.8, 14.10, 44.47

* *Triangular distribution parameters required for simulation: minimum, maximum. Beta-subjective distribution parameters required for simulation: minimum, mode, distribution-defined mean, maximum*

† *The mean returned by the simulation on the beta-subjective distribution, utilising the given distribution parameters*

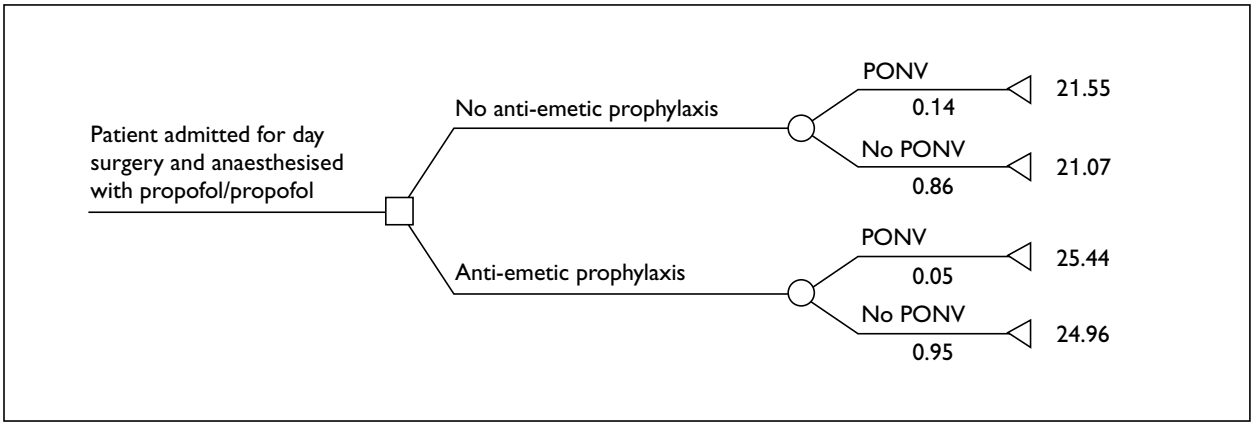

FIGURE 12 *The decision tree for simulating the effect of prophylactic ondansetron with the propofol/propofol regimen in the adult study*

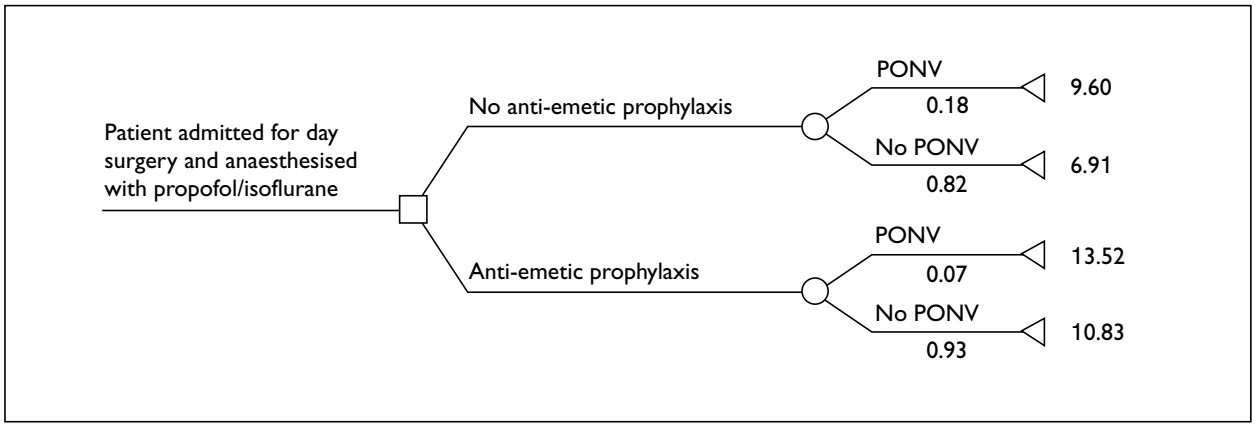

FIGURE 13 *The decision tree for simulating the effect of prophylactic ondansetron with the propofol/isoflurane regimen in the adult study*

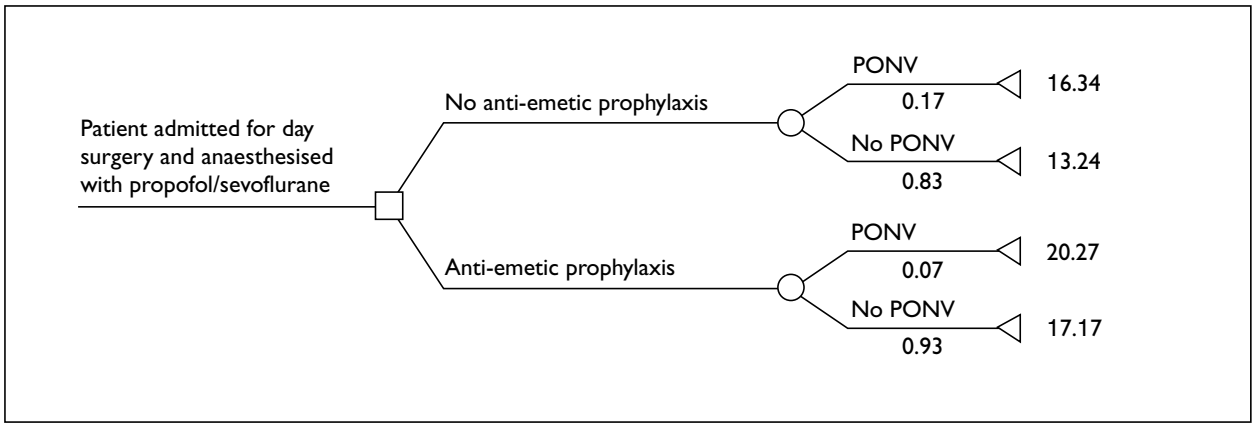

FIGURE 14 *The decision tree for simulating the effect of prophylactic ondansetron with the propofol/sevoflurane regimen in the adult study*

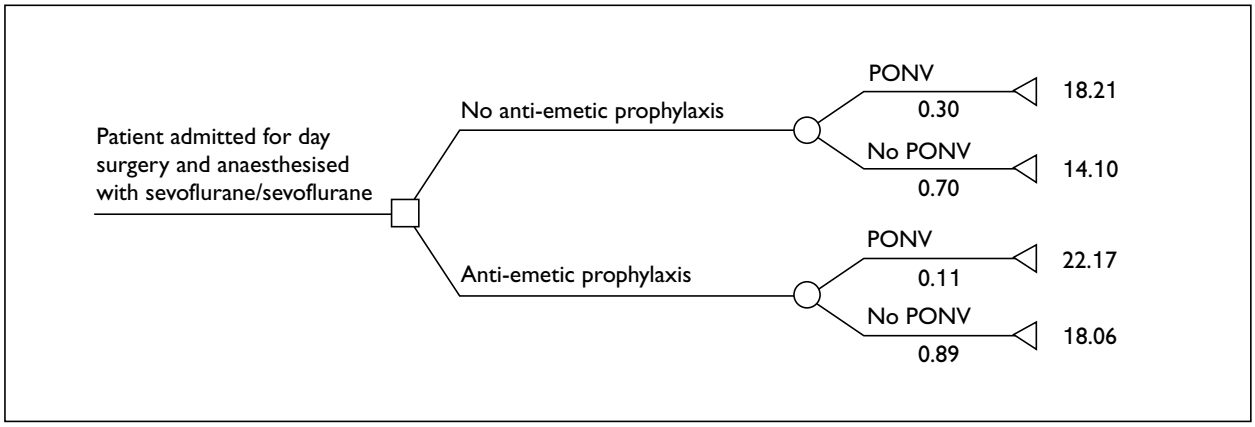

FIGURE 15 *The decision tree for simulating the effect of prophylactic ondansetron with the sevoflurane/sevoflurane regimen in the adult study*

TABLE 40 *Comparison of the variable cost per patient from the empirical study and the simulation for the adult study*

Anaesthetic regimen	Mean (SD) variable cost (£)	
	Empirical study	Simulation
Propofol/propofol	21.1 (12.2)	21.7 (11.4)
Propofol/sevoflurane	13.8 (11.7)	14.4 (8.1)
Propofol/isoflurane	7.4 (4.4)	7.2 (4.0)
Sevoflurane/sevoflurane	15.3 (6.8)	15.1 (5.6)

groups (ANOVA, F (3,705), 5.34; $p = 0.0012$). The sevoflurane/sevoflurane group had a significantly lower net benefit than did the propofol/isoflurane and the propofol/propofol groups (Tukey's HSD test, $p < 0.01$) (*Figure 16*).

Figure 17 shows the cumulative percentage of the net benefit/cost for each arm. The net cost was positive for around 15–25% of patients in the four study groups.

TABLE 41 *The results of the simulation for the case where all groups in the adult study receive prophylactic ondansetron*

Anaesthetic regimen	Variable cost per patient (95% CI) (£)	Patients with PONV (95% CI) (%)	ICER (£/PONV instance avoided)
Propofol/propofol	25.5 (24.7 to 26.3)	9.4 (6.4 to 12.4)	289*
Propofol/sevoflurane	17.7 (17.2 to 18.3)	12.1 (8.2 to 16.1)	3350†
Propofol/isoflurane	11.0 (10.7 to 11.2)	12.3 (8.2 to 16.4)	–
Sevoflurane/sevoflurane	18.9 (18.5 to 19.3)	20.3 (14.7 to 26.0)	Dominated

* *Calculated with respect to the propofol/sevoflurane regimen*
† *Calculated with respect to the propofol/isoflurane regimen*

TABLE 42 *The results of the simulation for the case where all groups in the adult study except the propofol/propofol group receive prophylactic ondansetron*

Anaesthetic regimen	Variable cost per patient (95% CI) (£)	Patients with PONV (95% CI) (%)	ICER (£/PONV instance avoided)*
Propofol/propofol	21.1	13.9 (9.8 to 18.1)	Dominated
Propofol/sevoflurane	17.7 (17.2 to 18.3)	12.1 (8.2 to 16.1)	3350
Propofol/isoflurane	11.0 (10.7 to 11.2)	12.3 (8.2 to 16.4)	–
Sevoflurane/sevoflurane	18.9 (18.5 to 19.3)	20.3 (14.7 to 26.0)	Dominated

* *Calculated with respect to the propofol/isoflurane regimen*

TABLE 43 *Net cost (£) by anaesthetic regimen in the adult study (invalid answers excluded)*

Net cost	Anaesthetic regimen				Total (n = 709)
	Propofol/ propofol (n = 178)	Propofol/ isoflurane (n = 189)	Propofol/ sevoflurane (n = 182)	Sevoflurane/ sevoflurane (n = 162)	
Mean (SD) total cost (£)	131.4 (88.9)	116.8 (79.8)	129.9 (99.3)	128.3 (72.8)	126.5 (85.8)
Mean (SD) net benefit (induction only, Net[I])	50.8 (286.1)	106.6 (245.4)	38.7 (209.4)	–23.3 (151.5)	45.6 (343.1)
Mean (SD) net benefit (maintenance only, Net[M])	324.5 (526.5)	265.8 (333.2)	271.3 (401.8)	185.1 (343.6)	263.0 (410.4)
Mean (SD) net benefit (induction and maintenance, Net[I + M])	507.3 (640.6)	489.1 (631.8)	440.8 (499.2)	289.0 (395.5)	435.5 (560.1)

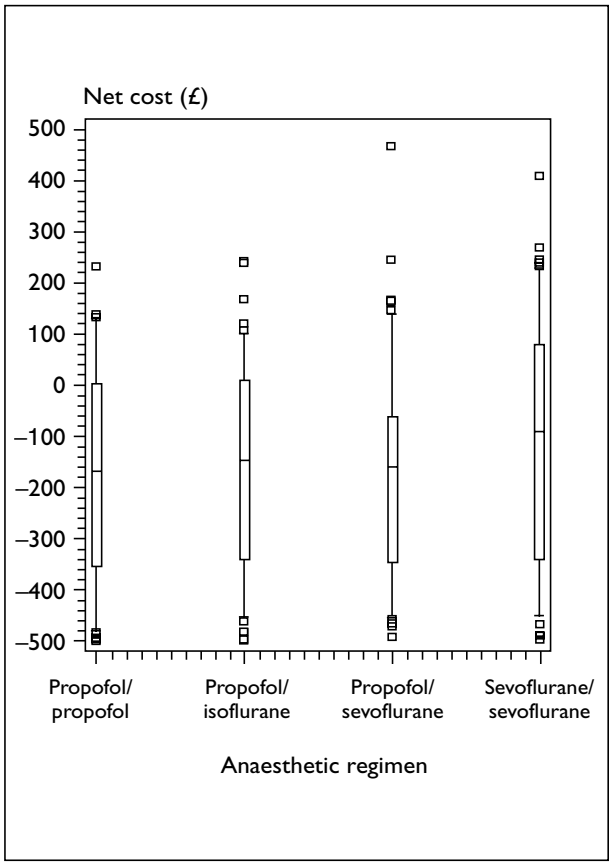

FIGURE 16 *The net cost for each anaesthetic regimen (limit 5% and 95% percentiles) in the adult study*

Summary

Recruitment

The overall recruitment rate was 73%, and 95 patients were withdrawn, providing 1063 patients for the study. Fifteen per cent of patients were lost to follow-up 7 days after discharge.

Clinical outcomes

Adults had a statistically significantly higher incidence of PONV with sevoflurane/sevoflurane than with propofol/propofol. Sevoflurane/sevoflurane was significantly different from propofol/volatile, but the difference between propofol/propofol and propofol/volatile was not significant.

The gender difference shown in previous studies was confirmed. The difference disappears with age and there was no gender difference in the paediatric study, and thus a premenopausal/ hormonal risk is implied. Additional risk factors associated with PONV are gynaecological surgery, agitation in recovery and duration of surgery.

The overall overnight admission rate was nearly 9%, which is quite high. However, this was due in part to the urology patients. In these patients high admission rates can be justified in some circumstances, as the patient is booked as a day-case but

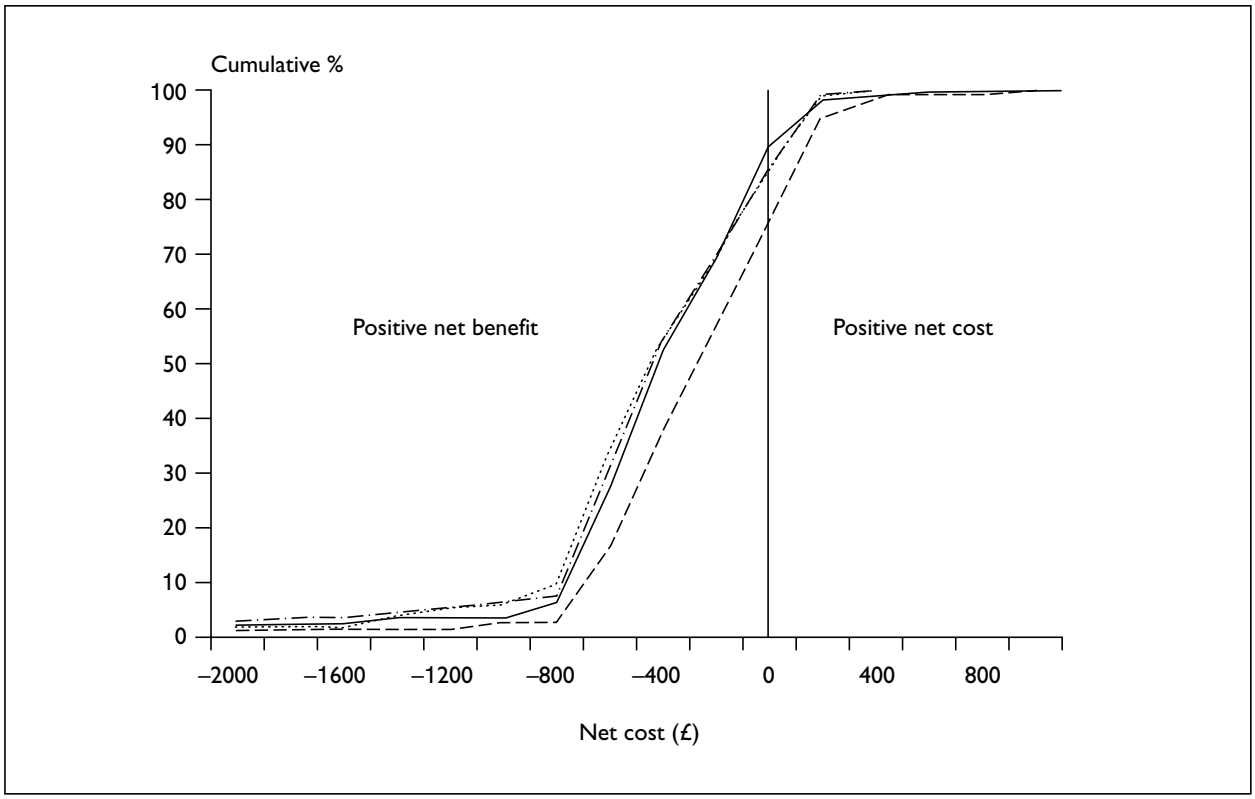

FIGURE 17 *The cumulative percentage of the net cost for each anaesthetic regimen in the adult study (– · – ·, propofol/propofol; ·····, propofol/isoflurane; ——, propofol/sevoflurane; – – –, sevoflurane/sevoflurane)*

with the express intention of admitting the patient overnight if the procedure is changed.

Resource use

The lengths of hospital stay and the total costs were not different between randomisation arms, but variable costs were significantly higher in the propofol/propofol group and significantly lower in the propofol/isoflurane group.

There were extremely low postdischarge costs to both the NHS and the patient, indicating that day-case discharge policies were clinically appropriate.

Patient preferences and CV

Patients who had not had inhalational induction before did not want it in the future. However, this changed after experience with a face mask in two-thirds of patients. On the whole patients were happy with the technique they received. This also suggests they could tell the difference between pre-oxygenation with a face mask and gas induction, because those who received pre-oxygenation and intravenous induction still did not want an inhalational induction.

With regard to CVs, those who chose inhalational induction placed a lower value on getting their choice than did those who chose intravenous induction.

There were no significant differences in CVs for induction or maintenance between the randomisation arms. There was also no significant difference in CVs for maintenance between those patients who had and those had not experienced PONV.

Cost-effectiveness analysis

Propofol/propofol was the most effective and most costly regimen (£21.10 per patient, PONV rate 14.0%). Sevoflurane/sevoflurane was the least effective regimen and was more costly than the mixed anaesthesia regimens (£15.30 per patient, PONV rate 29.9%).

The ICER for propofol/sevoflurane compared with propofol/isoflurane is £629.40 to avoid one PONV incident. The ICER for propofol/propofol compared with propofol/sevoflurane is £191.90 to avoid one PONV incident.

Sensitivity analysis

When the incidence of PONV was varied to its 95% CI, the rank order of the ICER did not change, indicating that the results of the study are robust in terms of the observed rate of PONV.

The cost-effectiveness plane demonstrated that the results of the baseline analysis for the empirical study were not robust with respect to observed PONV rates and variable costs for propofol/isoflurane compared with the results for propofol/propofol or propofol/sevoflurane.

The use of the Dion algebraic approximation for the use of volatile anaesthetic agents resulted in a systematic underestimation of anaesthetic agent use, although the estimation of a precise inflation factor proved difficult. It is likely that the inflation factor lies somewhere in the range 6–27%. The impact of this inflation factor was strongest for the sevoflurane/sevoflurane and propofol/sevoflurane regimens.

The modelled use of prophylactic ondansetron 4 mg intravenous in all groups resulted in propofol/sevoflurane having the largest ICER compared with propofol/isoflurane. Propofol/propofol remained the most costly and most effective regimen.

The modelled use of prophylactic intravenous ondansetron 4 mg in all groups except the propofol/propofol group resulted in propofol/propofol being the most costly regimen, but no longer the most effective. Propofol/sevoflurane had the largest ICER compared with propofol/isoflurane.

Net benefit

A significant difference in net benefit was found between randomisation arms. Net benefit was positive in all arms. Sevoflurane/sevoflurane had a lower net benefit than the other three regimens.

Chapter 6

Results of the paediatric economic evaluation

Recruitment to the CESA RCT

The study population was drawn from the patient population eligible for selected day-surgery procedures, who met the anaesthesia-based inclusion criteria for the trial. General and ENT procedures were the selected paediatric procedures.

During the recruitment period (October 1999 to January 2001), 480 paediatric patients attending for the selected day-surgery procedures were screened and 466 children were identified as eligible participants for the CESA RCT. The overall recruitment rate was 75% (347/466 patients identified as eligible) (see appendix 23 for reasons for non-participation). Twenty-five children were withdrawn from the study. A total of 322 paediatric patients (159 propofol/halothane, 163 sevoflurane/sevoflurane) remained in the study until discharge from hospital (see appendix 28). Nineteen per cent of paediatric patients were lost to follow-up 7 days after discharge. There was no difference in loss to follow-up between randomisation arms.

Numbers of patients

The number of paediatric patients in the study until hospital discharge, by individual study groups and randomisation arms, is summarised in *Table 44*.

Patient characteristics

The age of the paediatric patients by study group is summarised in *Table 45*. The age and surgical procedure received, by randomisation group, is

TABLE 44 *The number of patients in each study arm in the paediatric study*

Procedure, gender	Anaesthetic regimen		Total
	Propofol/ halothane	Sevoflurane/ sevoflurane	
Total	159	163	322
General, male	37	50	87
General, female	7	6	13
ENT, male	70	65	135
ENT, female	45	42	87

TABLE 45 *The age of patients in each group in the paediatric study*

Procedure, gender	No. of patients	Mean age (median, SD, range) (years)
Total	322	7.2 (6.6, 2.6, 2.9–13.0)
General, male	87	7.3 (7.1, 2.7, 2.9–13.0)
General, female	13	7.4 (6.7, 2.9, 4.0–12.6)
ENT, male	135	7.1 (6.5, 2.6, 2.9–12.9)
ENT, female	87	7.1 (6.2, 2.7, 3.0–13.0)

TABLE 46 *Patient characteristics by anaesthetic regimen in the paediatric study*[*]

Parameter	Anaesthetic regimen		Total
	Propofol/ halothane	Sevoflurane/ sevoflurane	
No. of patients	159	163	322
Mean age (SD, median, range) (years)	7.2 (6.6, 2.6, 3.0–13.0)	7.1 (6.7, 2.7, 2.9–12.9)	7.2 (6.6, 2.6, 2.9–13.0)
ASA grade I	137	132	269
ASA grade II	21	27	48
ASA grade III	1	1	2
ASA grade not known	0	3	3
Type of surgery			
Ear, minor	91	89	180
Penis	23	25	48
Gastrointestinal, intermediate	9	19	28
Throat, intermediate	16	8	24
Nose, minor	9	8	17
Scrotum/testes	3	7	10
Skin, minor	3	3	6
Tendons, muscles	2	2	4
Gastrointestinal, minor	3	0	3
Breast, throat, minor	0	2	2

[*] *See appendix 25*[261] *for surgical procedure classification and summary groups*

given in *Table 46*. All 322 patients were anaesthetised by physician anaesthetists. Within this, 12 consultant anaesthetists carried out 280 procedures and eight non-consultant anaesthetists carried out 42 procedures. The 322 patients were treated by eight surgeons.

Of 322 paediatric study participants' parents/guardians, 251 (78.0%) were married, 36 (11.2%) were separated, 31 (9.6%) were single, two were widowed and two did not answer. Employment details were recorded and categorised into social class for all male parents (employed and retired) of participants. In the case of single women, their own social class was recorded (*Table 47*).

TABLE 47 *The social class of the participants in the paediatric study*

Social class	No. of patients	British value (%)[248]
I	11 (3%)	5
II	53 (16%)	16
IIIN	43 (13%)	35
IIIM	42 (13%)	19
IV	48 (14%)	18
V	9 (2%)	6
Unemployed, student, housewife	116 (36%)	Not given

Clinical outcome data

PONV by anaesthetic regimen

The incidence of PONV was analysed to assess whether the risk of PONV differed between the anaesthetic regimens. First, the crude (unadjusted) figures were tabulated. Further tables in appendix 29 display the association between PONV and other variables that plausibly might be associated with risk. Logistic regression analysis was employed to confirm the impression portrayed by the tabular analyses. It was also used to adjust the estimates of PONV risk in order to allow for any residual effects of the potential confounding variables arising from them not being exactly evenly distributed across the randomisation arms. The total numbers of subjects shown in the tables vary slightly, since there are missing data for some of the variables. Probability values presented with tables refer, unless otherwise stated, to a simple test for heterogeneity among categories. So-called 'exact' tests were employed when appropriate. Probability values are not presented for tables examining the distribution of potential confounding variables among the randomisation categories, as the statistical significance of observed differences is not relevant to the question of confounding.

The randomisation of children occurred within two strata defined by gender. *Table 48* displays the occurrence of PONV by anaesthetic regimen within each of the gender strata. It is apparent that within each stratum the risk of occurrence of PONV was greatest under the sevoflurane/sevoflurane regimen.

Tables 49 to *51* display the occurrence of PONV by severity in the two anaesthesia categories. The occurrence of PONV is greater in the sevoflurane/sevoflurane group (ORs, compared to propofol/halothane, of 2.9 and 4.1 for 'nausea or vomiting' and 'one or more episodes of vomiting' respectively). Two or more episodes of vomiting were too infrequent to bear separate analysis.

Other adverse events

Table 52 summarises the degree of orientation of patients during recovery from the anaesthesia. There was a statistically significant difference in the degree of orientation between the two anaesthetic regimens.

TABLE 48 *The occurrence of PONV by anaesthetic regimen in the two predefined strata in the paediatric study*

Stratum	PONV	Anaesthetic regimen		Total
		Sevoflurane/sevoflurane	Propofol/halothane	
Male	No	96 (83.5%)	101 (94.4%)	197 (88.7%)
	Yes	19 (16.5%)	6 (5.6%)	25 (11.3%)
	Total	115 (100.0%)	107 (100.0%)	222 (100.0%)
Female	No	43 (89.6%)	49 (94.2%)	92 (92.0%)
	Yes	5 (10.4%)	3 (5.8%)	8 (8.0%)
	Total	48 (100.0%)	52 (100.0%)	100 (100.0%)

TABLE 49 *The occurrence of any PONV by anaesthetic regimen in the paediatric study*

	Anaesthetic regimen		Total
	Propofol/halothane	Sevoflurane/sevoflurane	
Total No. of patients	159 (100%)	163 (100%)	322 (100%)
Nausea or vomiting – no	150 (94.3%)	139 (85.3%)	289 (89.8%)
Nausea or vomiting – yes	9 (5.7%)	24 (14.7%)	33 (10.2%)
$p < 0.01$			

TABLE 50 *The occurrence of one or more episodes of PONV by anaesthetic regimen in the paediatric study*

	Anaesthetic regimen		Total
	Propofol/halothane	Sevoflurane/sevoflurane	
Total No. of patients	159 (100%)	163 (100%)	322 (100%)
One or more episodes of vomiting – no	156 (98.1%)	151 (92.6%)	307 (95.3%)
One or more episodes of vomiting – yes	3 (1.9%)	12 (7.4%)	15 (4.7%)
$p < 0.01$			

TABLE 51 *The occurrence of two or more episodes of PONV by anaesthetic regimen in the paediatric study*

	Anaesthetic regimen		Total
	Propofol/halothane	Sevoflurane/sevoflurane	
Total No. of patients	159 (100%)	163 (100%)	322 (100%)
Two or more episodes of vomiting – no	158 (99.4%)	161 (98.8%)	319 (99.1%)
Two or more episodes of vomiting – yes	1 (0.6%)	2 (1.2%)	3 (0.9%)

TABLE 52 *The degree of orientation in recovery by anaesthetic regimen in the paediatric study*

Degree of orientation	Total No. of patients	Anaesthetic regimen	
		Propofol/halothane	Sevoflurane/sevoflurane
Total No. of patients	322	159	163
Alert	199	98	101
Agitated*	57	15	42
Drowsy†	65	45	20
Not known	1	1	0

* $\chi^2 = 14.74$, $p < 0.001$
† $\chi^2 = 12.84$, $p < 0.001$

Other adverse events were recorded in the anaesthetic room, operating theatre, recovery room and ward. There was a low incidence of adverse events overall, and these are summarised in appendix 30. There was no difference between randomisation arms.

Previous anaesthetic experience

Parents/guardians reported a mean of 0.9 previous anaesthetic experiences (median 0.5, SD 1.5, range 0–10). There was no difference between the randomisation arms in this respect.

Logistic regression analysis of PONV

Logistic regression was employed using as the binary dependent variable either the presence/absence of any nausea or vomiting or the presence/absence of one or more episodes of vomiting. These analyses are not wholly independent of one another, but they serve to elucidate some of the fine detail of the

patterns in the data and to adjust the estimates of the risks of PONV among the various anaesthetic regimens. The independent variables explored were anaesthetic regimen (categorical), age (numeric), gender (categorical), orientation (categorical), duration of anaesthesia (numeric), ASA grade (categorical), previous anaesthetics (numeric) and surgical procedure (categorical).

The analysis was performed in an exploratory manner (informed by the findings from the tables) rather than merely letting the analytic routine find the best fitting, and not necessarily most informative, model. The final model selected (see below) turned out to be the best fitting, most parsimonious and intuitively most appealing among several candidate models.

Logistic regression analysis confirmed the tabular analyses. None of the variables, other than anaesthetic regimen, made any contribution to the fit of the model. Thus the best estimate of the ORs is as calculated from *Table 53*, which also gives the associated 95% CIs.

Resource use data

Table 54 summarises the length of stay and the principal cost parameters of the paediatric patients. *Figure 18* shows the distribution of the length of stay data. No statistically significant differences were found between these factors for the different anaesthetic regimens ($p = 0.867$).

There were four overnight stays (1.2%), two of which were general male and two of which were ENT male patients. There were two overnight stays in each randomisation arm. The reasons for these overnight stays were more extensive surgery, hypoglycaemia, organisational reasons and bleeding.

The total costs include all costs from the NHS perspective, including postdischarge costs (e.g. readmission, GP visits). Variable costs exclude staff, fixed and postdischarge costs. Sevoflurane/sevoflurane had significantly higher total costs ($p < 0.0001$) and variable costs ($p = 0.0001$) than did propofol/halothane. For the distribution of the variable costs data, see *Figures 19* and *20*.

Postdischarge NHS costs and parents'/guardians' own costs were obtained from 260 respondents who were followed up with a telephone interview at day 7. Postdischarge costs and self-care costs incurred by parents/guardians postdischarge are summarised in *Table 54*. Postdischarge NHS costs and patients' own costs were minimal and did not differ between anaesthetic regimens.

TABLE 53 *ORs for PONV in the paediatric study*

Outcome	Anaesthetic regimen	OR (95% CI)
Nausea or vomiting	Sevoflurane/sevoflurane vs propofol/halothane	2.88 (1.29 to 6.40) 1 (NA)
Any vomiting	Sevoflurane/sevoflurane vs propofol/halothane	4.13 (1.14 to 14.9) 1 (NA)

Parent/guardian preferences and CV data

The preference and CV data were from the parents/guardians of children in the CESA RCT. These were obtained by telephone interview 7 days postoperatively.

Preference for induction of anaesthesia

The 260 parents/guardians of the children included in the CESA RCT were asked for a

TABLE 54 *Length of stay and principal cost parameters in the paediatric study*

Parameter	Propofol/halothane (*n* = 159)	Sevoflurane/sevoflurane (*n* = 163)	Total (*n* = 322)
Mean (SD) length of stay (h)	5.2 (2.4)	5.1 (1.9)	5.1 (2.2)
Mean (SD) total cost (£)	84.0* (21.2)	94.5* (24.7)	89.3 (23.6)
Mean (SD) variable cost (£)	3.5* (1.9)	12.4* (5.9)	8.0 (6.3)
Parents' own costs (SD) (£)	0.04 (0.26) (*n* = 125)	0.03 (0.18) (*n* = 135)	0.04 (0.22) (*n* = 260)
Postdischarge NHS costs (SD) (£)	2.3 (8.3) (*n* = 125)	3.6 (12.7) (*n* = 135)	3.0 (10.8) (*n* = 260)

* p = *0.0001*

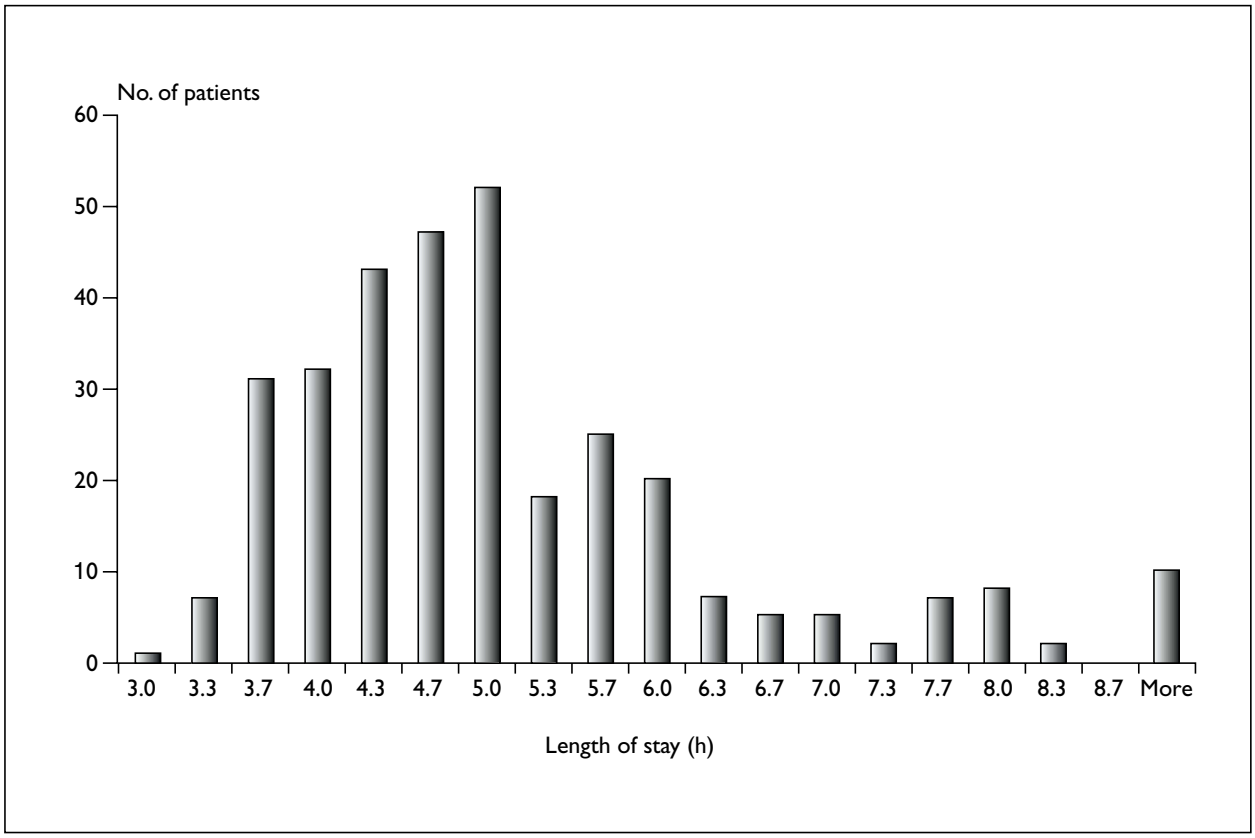

FIGURE 18 *The length of stay of patients in the paediatric study*

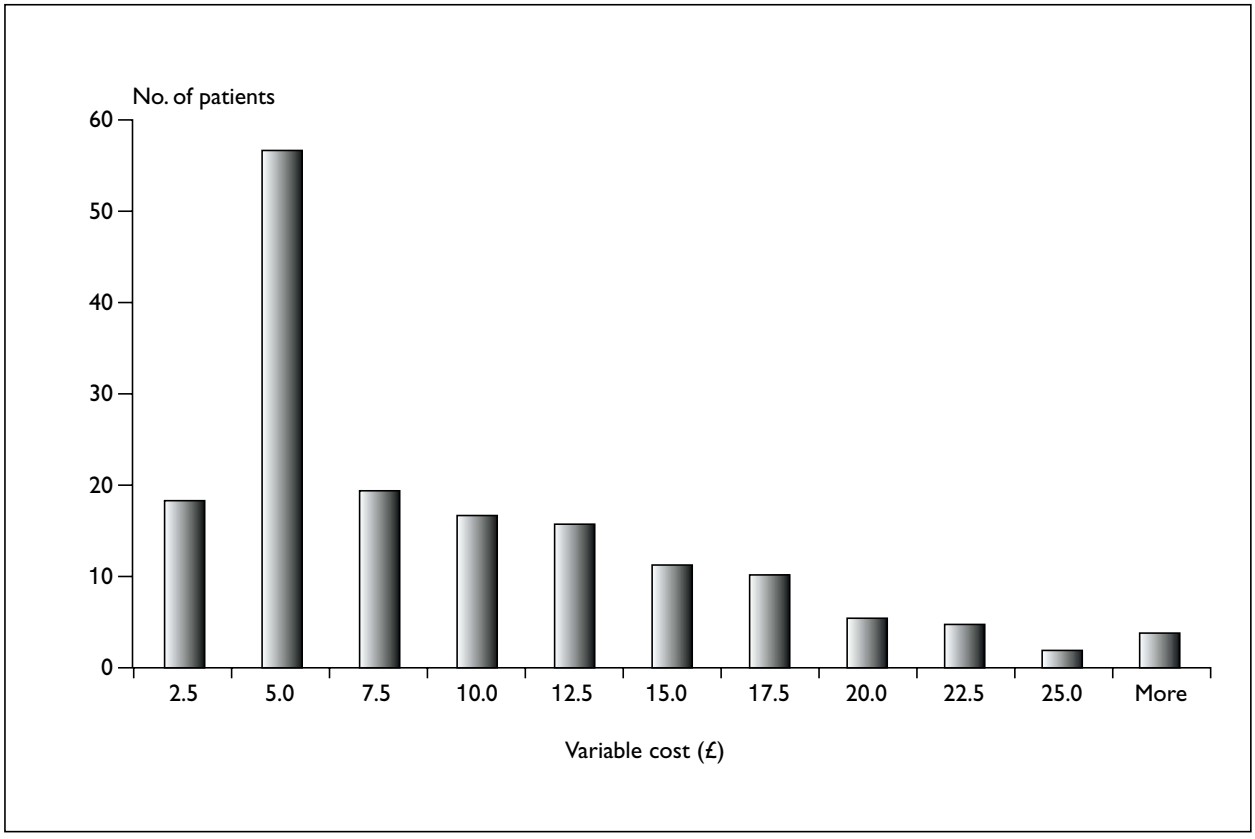

FIGURE 19 *Distribution of the variable costs of patients in the paediatric study*

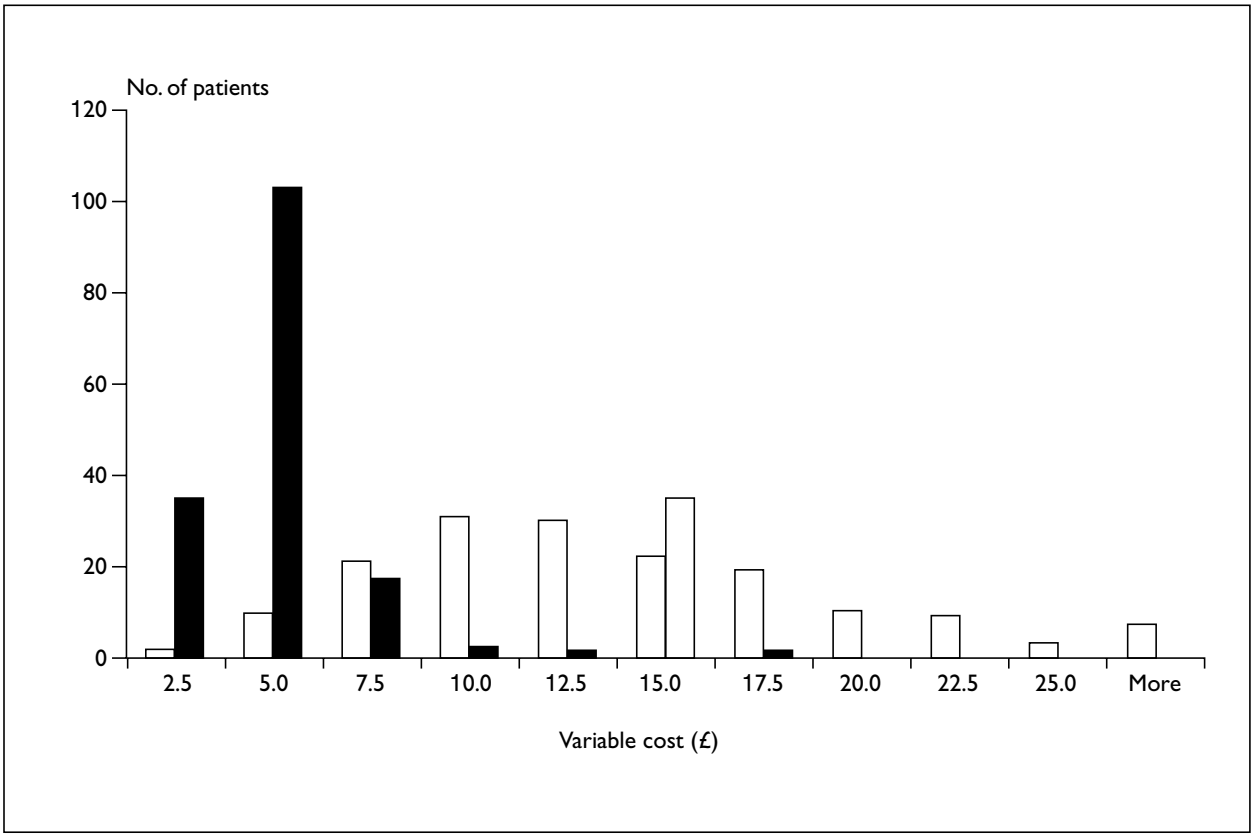

FIGURE 20 *Distribution of the variable costs of patients by anaesthetic regimen in the paediatric study (□, sevoflurane/sevoflurane; ■, propofol/halothane)*

preference for intravenous (scenario A) or inhalational (scenario B) induction anaesthesia (*Table 55*). The results show that 66% of parents whose children had received intravenous induction would prefer that method in the future to inhalational induction. Of parents whose children had received inhalational induction, 80% would prefer that method in the future to intravenous induction. This suggests that the parents would prefer the method of induction with which they feel more familiar, although 56% parents who were followed up favoured the inhalational method overall.

CVs for induction of anaesthesia

Parents were asked to give a value for their expressed preference. Parents who gave valuations that were classed as invalid (see appendix 16) were excluded from the analysis. A minority of parents who gave responses of 'more than £250' but did not give an actual value, were also excluded. Responses from 228 parents/guardians were used in this analysis. *Table 56* summarises the CVs given by parents for induction anaesthesia for the different anaesthetic regimens. The mean CVs were not significantly higher for inhalational induction than for intravenous induction ($p = 0.3065$). The mean CVs were not significantly higher for intravenous induction or for inhalational induction between the intravenous or inhalational induction randomisation arms ($p = 0.3192$, $p = 0.0989$). Excluding invalid responses had no significant effect on the summary values (data not shown).

Figure 21 shows the distribution of CVs for induction anaesthesia. It is clear that there is

TABLE 55 *The incidence of a preference for intravenous (scenario A) or inhalational (scenario B) induction anaesthesia by anaesthetic regimen in the paediatric study*

Anaesthetic regimen	Total No. of patients	Preference for scenario A	Preference for scenario B	No preference	Not answered	Lost to follow-up
Total No. of patients	322	113	146	1	0	62
Propofol/halothane	159	88	44	1	0	–
Sevoflurane/sevoflurane	163	25	102	0	0	–

TABLE 56 *CVs for induction with intravenous anaesthetic (scenario A) or inhalational anaesthetic (scenario B), by anaesthetic regimen in the paediatric study (invalid answers excluded)*

Anaesthetic regimen	No. who chose scenario A	Mean (median, SD, range) CV for scenario A (£)	No. who chose scenario B	Mean (median, SD, range) CV for scenario B (£)
Total No. of patients	97	221.4 (200, 177, 0–1000)	131	255.2 (200, 259, 0–2000)
Propofol/halothane	77	227.3 (200, 191, 0–1000)	42	207.1 (187.5, 200, 0–1000)
Sevoflurane/sevoflurane	20	198.8 (225, 107, 0–500)	89	277.8 (200, 280, 0–2000)

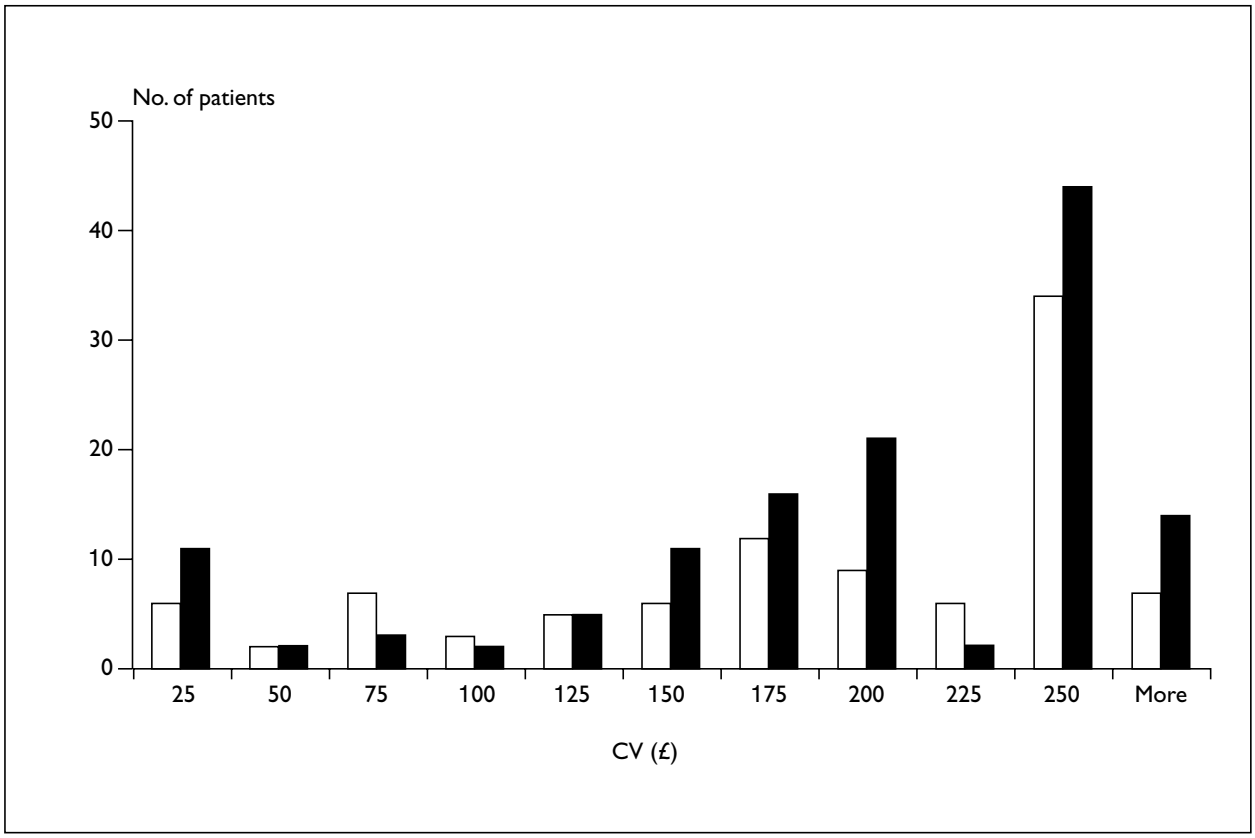

FIGURE 21 *Distribution of the CVs for induction with intravenous anaesthetic (scenario A) or inhalational anaesthetic (scenario B) in the paediatric study (□, scenario A; ■, scenario B)*

a scale effect for scenario A, but not for scenario B, which was not evident in the piloting work. Many parents' responses appear to have been constrained by the scale, despite pilot work and the option to provide a value beyond the limits of the scale. This suggests that the more recent the experience of anaesthesia, the stronger the preferences expressed. It also suggests that the CVs reported here are conservative rather than extravagant values.

Parents' preferences for maintenance of anaesthesia

The parents/guardians of the 260 children in the CESA RCT were asked for their preference for scenario C or scenario D (*Table 57*). The results show that 98% of parents would choose the scenario where the risk of PONV was reduced. Those parents who picked scenario C were considered to have given invalid answers and were excluded from the analysis.

CVs for maintenance of anaesthesia

Parents were asked to give a value for their expressed preference. Parents who gave valuations that were classed as invalid (see appendix 16) were excluded from the analysis. A minority of parents who gave responses of 'more than £250' but did not give an actual value were also excluded. A total of 236 responses were used in this analysis. *Table 58* summarises the CVs given by parents for maintenance anaesthesia, by randomisation group.

TABLE 57 *The incidence of preference for a PONV risk of 7/10 (scenario C) or 3/10 (scenario D), by anaesthetic regimen in the paediatric study*

Anaesthetic regimen	Total No. of patients	Preference for scenario C	Preference for scenario D	No preference	Not answered	Lost to follow-up
Total No. of patients	322	3	254	2	1	62
Propofol/halothane	159	2	129	1	1	–
Sevoflurane/sevoflurane	163	1	125	1	0	–

TABLE 58 *CVs for maintenance anaesthesia with a PONV risk of 7/10 (scenario C) or 3/10 (scenario D), by anaesthetic regimen in the paediatric study (invalid answers excluded)*

Anaesthetic regimen	No. who chose C	No. who chose D	Mean (SD) CV for D (£)	Mean (SD) CV x 2.5 for D (£)
Total No. of patients	3	236	237.7 (194)	594.5 (485)
Propofol/halothane	2	120	222.4 (148)	556.1 (370)
Sevoflurane/sevoflurane	1	116	253.7 (232)	634.2 (579)

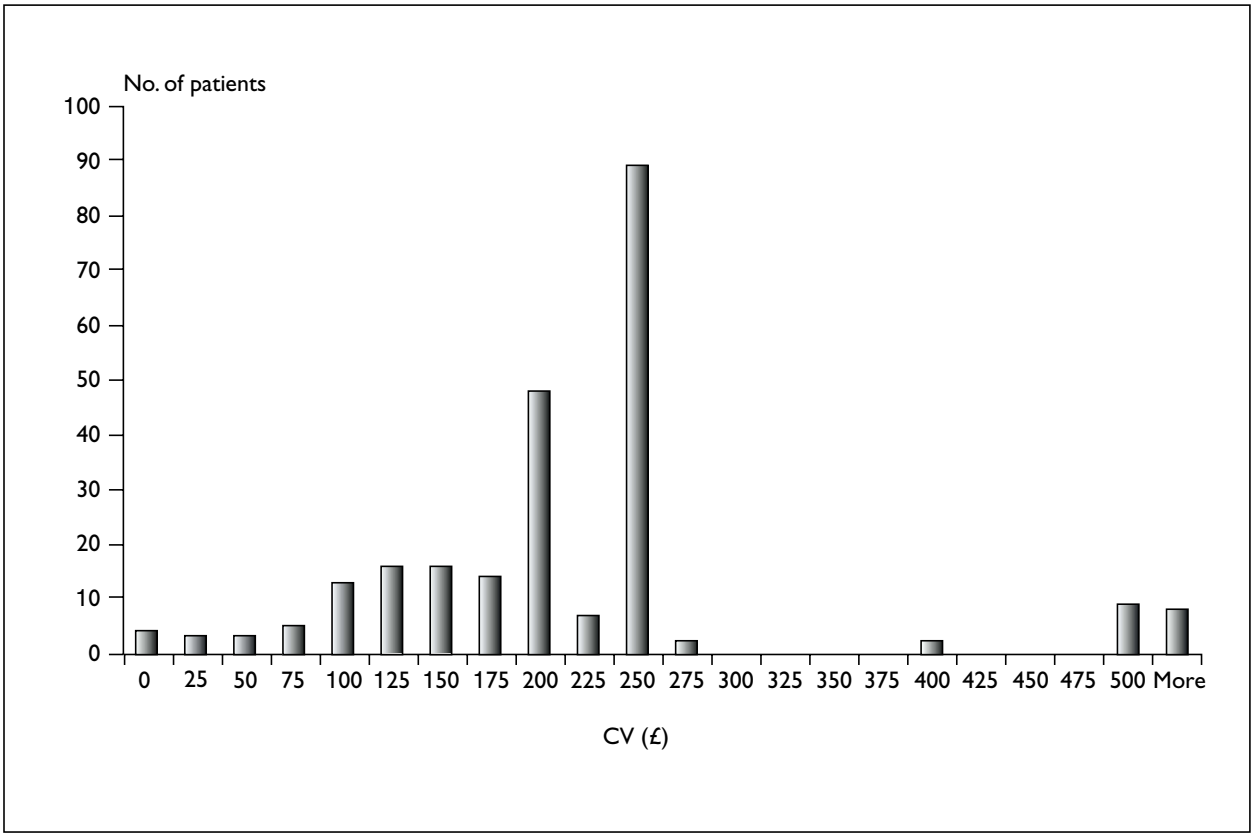

FIGURE 22 *Distribution of CVs for avoidance of PONV after maintenance anaesthesia (scenario D) in the paediatric study*

The mean CVs for avoidance of PONV were not significantly lower in the propofol/halothane group ($p = 0.2633$).

The mean CV for those parents whose children suffered, and who did not suffer, PONV was £199.0 (SD = £117.4, $n = 24$) and £245.7 (SD = £208.7, $n = 194$) ($p = 0.105$). Therefore, the CV of parents was not affected by their experience of the clinical outcome. The conclusion was not altered when CVs were corrected by a factor of 2.5.

Figure 22 shows the distribution of CVs for maintenance anaesthesia. It is clear that there is been a scale effect for scenario D.

Reported income bands

Table 59 summarises the reported monthly income bands of the parents of the participants in the paediatric study. There was no difference in income distribution between the randomisation arms.

Income was not correlated with CVs (CVs for induction, Spearman's ρ = 0.1305, $p = 0.0590$; CVs for maintenance, Spearman's ρ = 0.1210, $p = 0.080$) (*Figures 23* and *24*).

TABLE 59 *Reported monthly household income bands of the parents of the participants in the paediatric study*

Monthly household income	No. of patients
> £2000	39 (12.4%)
£1001 to £2000	97 (30.9%)
£501 to £1000	63 (20.1%)
£250 to £500	47 (15.0%)
< £250	6 (1.9%)
Income not given	8 (2.5%)
Lost to follow-up	62 (19.7%)

Incremental cost-effectiveness ratios

In order to determine if there was a significant difference in the primary clinical outcome measure (frequency of PONV) it was necessary to derive the ICERs for the two randomisation arms. However, the cost of the more effective anaesthetic regimen is lower, and therefore propofol/halothane is the dominant arm (*Table 60*). The use of the propofol/halothane regimen reduced the variable costs by £1464.70 and the frequency of PONV by 15 episodes.

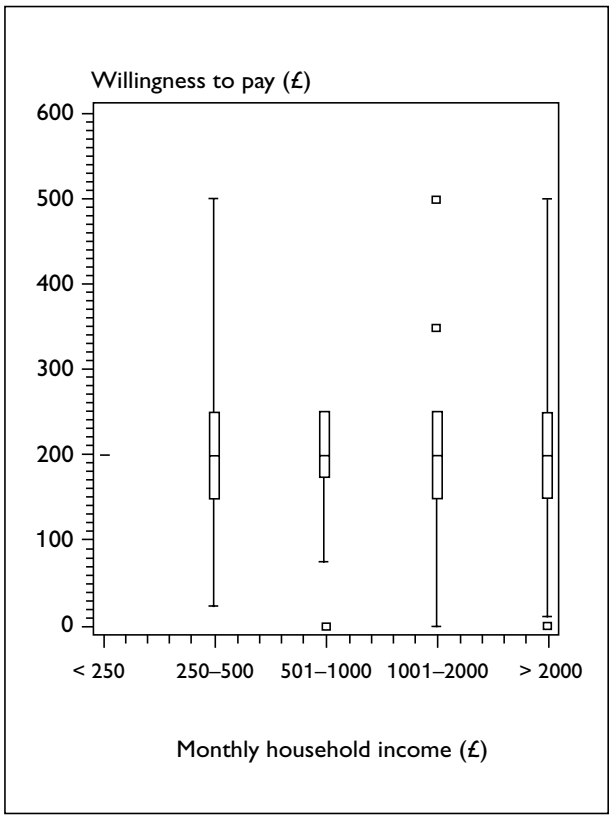

FIGURE 23 *Willingness to pay for induction anaesthesia versus monthly household income (limit 5% and 95% percentiles) in the paediatric study*

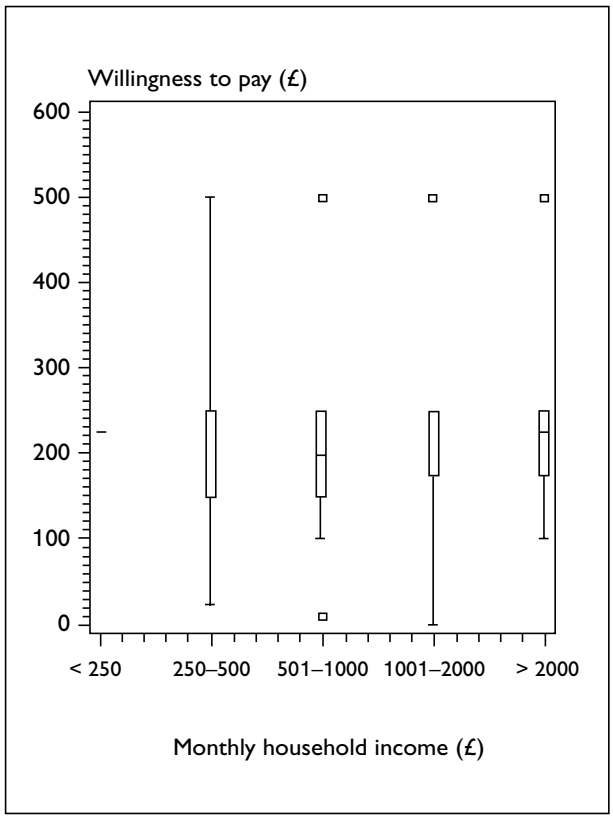

FIGURE 24 *Willingness to pay for maintenance anaesthesia versus monthly household income (limit 5% and 95% percentiles) in the paediatric study*

TABLE 60 *Costs and outcomes by anaesthetic regimen in the paediatric study*

Anaesthetic regimen	Total variable cost for group (mean per patient) (£)	No. of patients with PONV
Propofol/halothane	556.5 (3.5)	9 (5.6%)
Sevoflurane/ sevoflurane	2021.2 (12.4)	24 (16.5%)

Sensitivity analysis

Uncertainty: CESA RCT data

Clinical outcomes

The impact of uncertainty around clinical outcomes was tested using a deterministic sensitivity analysis on the observed rate of PONV. In the deterministic sensitivity analysis, extreme values are taken for a named parameter individually, in order to examine the effects on the ICER found in the baseline analysis of the empirical study.

The extreme (lower and upper) values for the probability of PONV were defined using 95% CIs around the observed PONV rate.

Table 61 shows the results of a deterministic sensitivity analysis on the observed rate of PONV. The modelled baseline values for the ICERs closely match the values found in the empirical study. The two sets of values do not match exactly due to arithmetic rounding. This sensitivity analysis shows that the results of the empirical study are robust in terms of the observed PONV rate.

TABLE 61 *Deterministic sensitivity analysis on the rate of PONV in the paediatric study*

Parameter	Anaesthetic regimen	
	Propofol/ halothane (*n* = 159)	Sevoflurane/ sevoflurane (*n* = 163)
Mean cost per patient with PONV (£)	4.6	14.8
Mean cost per patient with no PONV (£)	3.5	12.0
Probability of PONV	0.06 (low 0.02; high 0.10)	0.15 (low 0.10; high 0.20)
Probability of no PONV (= 1 – probability of PONV)	0.94	0.85
Expected variable cost per patient (£)	3.69 (low 3.64; high 3.74)	12.42 (low 12.28; high 12.56)

Bootstrapped distributions of ICERs

Bootstrapped distributions of the ICERs were generated for propofol/halothane compared with sevoflurane/sevoflurane (*Figure 25*). The cost-effectiveness plane generated (2.5% and 97.5% percentiles –£32 and –£5, respectively) confirms the conclusion that propofol/halothane is the dominant arm.

Substitution of isoflurane or sevoflurane for halothane

The national survey suggested that the use of halothane in paediatric maintenance anaesthesia has declined (see chapter 3). It is likely that halothane will be, or is being, superseded by isoflurane or sevoflurane. Therefore, the impact of substituting isoflurane or sevoflurane in the propofol/halothane regimen was investigated through simple modelling.

It was not satisfactory to assume that a quantity (in millilitres) of one anaesthetic was equivalent to another (i.e. 5 ml sevoflurane is not equivalent to the administration of 5 ml halothane). To mirror actual practice as closely as possible, it was assumed that the clinical endpoint aimed for by administration of a volatile anaesthetic in the anaesthetic room or in the operating theatre determined the quantity of volatile anaesthetic given. It was thus assumed that an equivalent MAC of anaesthetic would be given to achieve that clinical endpoint, irrespective of the particular anaesthetic given. MACs of oxygen for children were obtained from the product datasheets and were used to provide a standard measure of the dose of volatile anaesthetic administered. The MACs used were 1.08% for halothane,[260] 1.6% for isoflurane[260] and 2.4% for sevoflurane[260] (values for children). The following relationship was assumed:

$$\frac{\%\ \text{Concentration of halothane administered}}{\text{MAC halothane}} = \frac{\%\ \text{Concentration [volatile}_2\text{] administered}}{\text{MAC [volatile}_2\text{]}}$$

where volatile$_2$ was either isoflurane or sevoflurane. This relationship was used to convert the percentage concentration of halothane administered to the percentage concentration of sevoflurane and percentage concentration of isoflurane at each time interval.

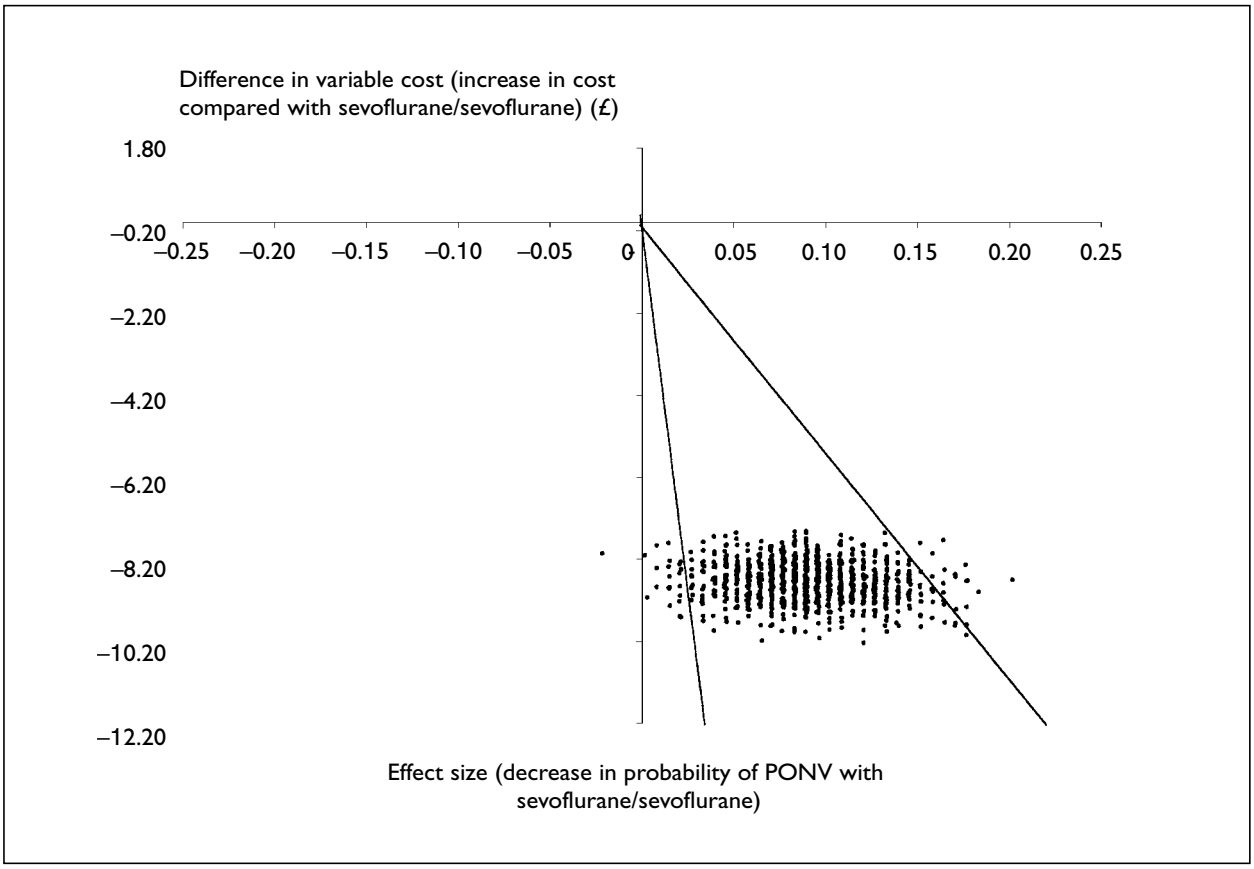

FIGURE 25 *The cost-effectiveness plane for propofol/halothane versus sevoflurane/sevoflurane (the 2.5% and 97.5% percentile boundaries are indicated by the straight line from the origin) in the paediatric study*

TABLE 62 *Sensitivity analysis: modelling the effect on costs of substituting isoflurane and sevoflurane for halothane in the paediatric study (n = 159)*

Cost	Anaesthetic regimen		
	Propofol/halothane, observed costs	**Propofol/isoflurane, modelled costs**	**Propofol/sevoflurane, modelled costs**
Mean (SD) total cost (£)	84.0 (21.2)	84.8 (21.4)	93.5 (23.7)
Mean (SD) variable cost (£)	3.5 (1.9)	4.4 (2.0)	13.0 (6.6)

The new variable cost and total cost per patient were calculated. The results are listed in *Table 62*.

Derivation of ICERs

There is no strong evidence to suggest that the PONV rates will differ between halothane, isoflurane or sevoflurane when these agents are given in conjunction with propofol (see chapter 2). Therefore, the outcomes were assumed to be the same as in the observed dataset. *Table 63* shows the total variable costs and PONV rates for the groups for the observed and modelled alternatives. It can be seen that substituting halothane with isoflurane has a small effect on costs, but does not alter the conclusion that propofol with an inhalational

TABLE 63 *Modelled costs and outcomes for the different anaesthetic regimens in the paediatric study*

Anaesthetic regimen	Total variable cost for group (£)	No. of patients with PONV (%)
Propofol/halothane, observed	556.5	9 (5.6%)
Sevoflurane/sevoflurane, observed	2021.2	24 (16.5%)
Propofol/isoflurane, modelled	699.6	9 (5.6%)
Propofol/sevoflurane, modelled	2067.0	9 (5.6%)

agent dominates sevoflurane/sevoflurane. It can be seen that substituting halothane with sevoflurane has a larger effect on costs, such that this arm is now more costly as well as more effective. The ICER derived for propofol/sevoflurane compared with sevoflurane/sevoflurane is £3.10 for each extra PONV episode avoided.

Use of the Dion algebraic approximation

Variable costs for patients who received sevoflurane were recalculated using the same methods used in the analysis in the adult study, using inflation factors of 6% (anaesthetic room) and 14% (operating theatre) (see appendix 18). The mean (SD) variable cost per patient increased from £12.40 (5.90) to £13.40 (6.50). However, the rank order of the alternatives does not change, so the conclusions regarding cost-effectiveness do not change from those in the base case.

Net benefit

The net benefit was calculated in the same way as in the adult study (see chapter 4). Net benefit (called 'net cost') was calculated only for those parents who had given a valid CV for both scenarios (n = 217). *Table 64* summarises the net cost by anaesthetic regimen for:

- mean net cost (induction only, Net[I])
- mean net cost (maintenance only, Net[M])
- mean net cost (induction and maintenance, Net[I + M]).

No significant difference in net cost (Net[I + M]) was found between anaesthetic regimens (p = 0.1007) (*Figure 26*). The net benefit for both propofol/halothane and sevoflurane/sevoflurane was positive. This result apparently contradicts the net savings and higher effectiveness of propofol/halothane in the cost-effectiveness analysis. The direction and magnitude of parents' preferences for their child to have an inhalational induction are responsible for this disagreement in results between the two economic evaluations. This suggests that parents do not consider the clinical outcome measure (PONV) to be as important as the method of administration of anaesthetic.

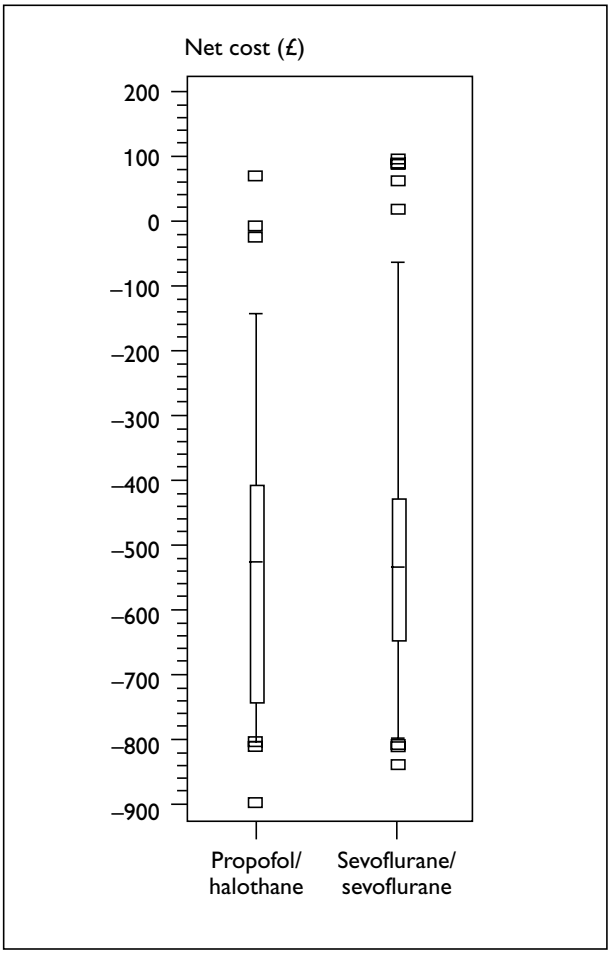

FIGURE 26 *The net cost for each anaesthetic regimen (limit 5% and 95% percentiles) in the paediatric study*

Figure 27 shows the cumulative percentage of the net cost for each anaesthetic regimen. The net benefit was positive for over 90% of patients in both groups.

TABLE 64 *Net cost by randomisation (excluding invalid answers) (paediatric study)*

Net cost	Anaesthetic regimen		Total (n = 217)
	Propofol/halothane (n = 112)	Sevoflurane/sevoflurane (n = 105)	
Mean (SD) total cost (£)	85.1 (24.3)	97.3 (25.8)	91.0 (25.7)
Mean (SD) net cost (induction only, Net[I])	–62.3 (194.1)	–129.4 (285.1)	–94.8 (244.2)
Mean (SD) net cost (maintenance only, Net[M])	–486.7 (388.6)	–573.3 (652.7)	–525.5 (524.1)
Mean (SD) net cost (induction and maintenance, Net[I + M])	–638.8 (505.1)	–812.1 (927.3)	–716.9 (729.5)

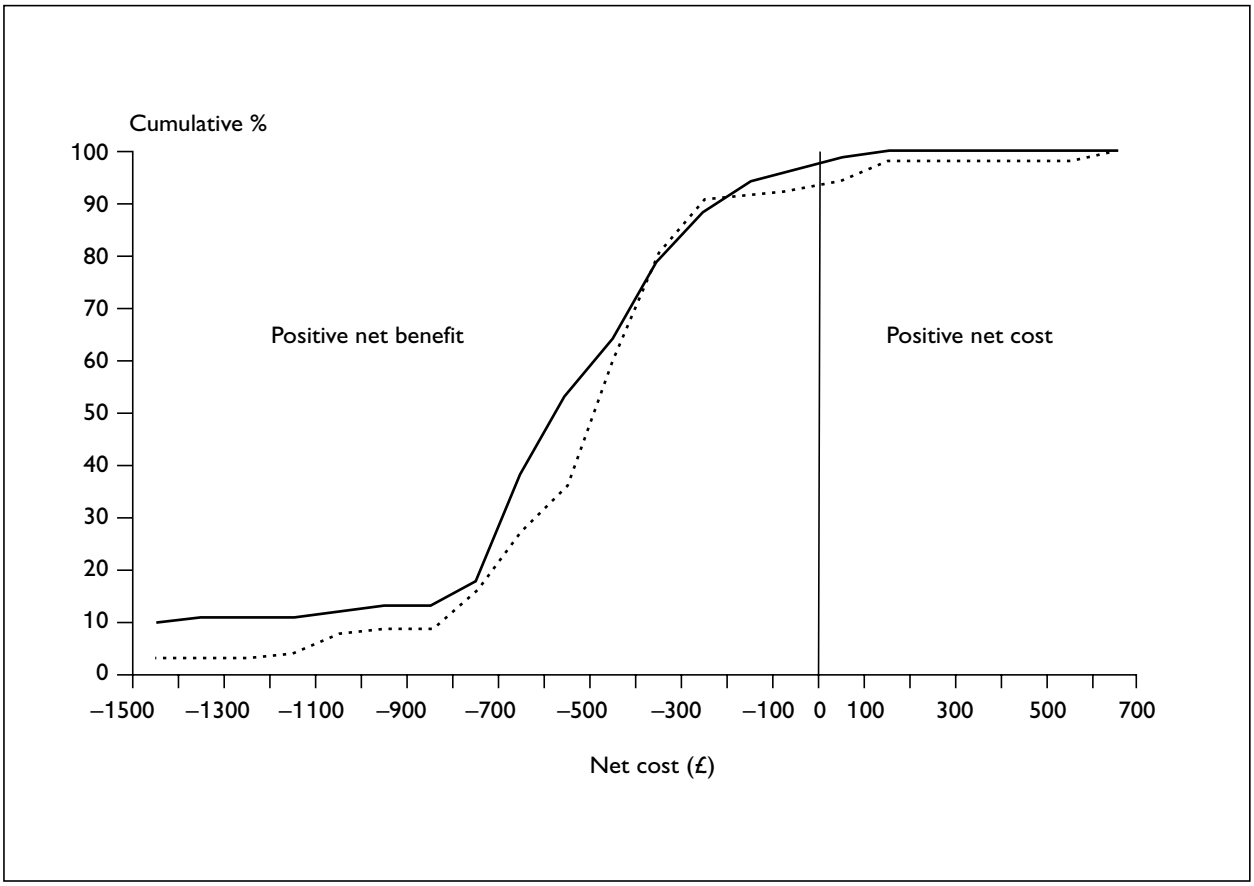

FIGURE 27 *The cumulative percentage of the net cost for each anaesthetic regimen in the paediatric study (——, sevoflurane/sevoflurane; - - -, propofol/halothane)*

Summary

Recruitment

The overall recruitment rate was 75%, and 25 patients were withdrawn, providing 322 patients in the study. Nineteen per cent of patients were lost to follow-up 7 days after discharge.

Clinical outcomes

- Children were significantly more sick with sevoflurane/sevoflurane than with propofol/halothane.
- No gender difference was found in terms of the rate of PONV. An additional risk factor associated with PONV is agitation in recovery.
- The overall overnight admission rate was only 1.2%.

Resource use

- The length of hospital stay was not different between randomisation arms, but variable costs and total costs were significantly higher in the sevoflurane/sevoflurane arm.
- There were extremely low postdischarge costs to both the NHS and the parents, demonstrating that day-surgery discharge policies were clinically appropriate.

Patient preferences and CV

- Parents whose children had not had the mask (sevoflurane) before did not want it in the future. Parents whose children had not had the injection (propofol) before did not want it in the future. On the whole, parents were happy with the technique their children received.
- Those parents who would choose the same induction method in the future as that which their child had received tended to give higher CVs than those who chose the alternative method for induction, but the differences were not statistically significant.
- Parents did not give higher CVs for avoiding PONV if their child had received sevoflurane/sevoflurane. Parents gave higher CVs for their children to avoid PONV than did the adult patients to avoid PONV themselves.
- There was no significant difference in CVs for maintenance anaesthesia between those parents whose children had and had not experienced PONV.

Cost-effectiveness analysis

Propofol/halothane was the most effective and least costly (£3.50 per patient, rate of

PONV 5.7%), compared with sevoflurane/sevoflurane which was the least effective and most costly (£12.40 per patient, rate of PONV 14.7%). The former alternative is therefore the dominant arm.

Sensitivity analysis

- When the incidence of PONV was varied to its 95% CIs, the results of the baseline analysis for the empirical study were shown to be robust with respect to the observed PONV rate.
- Generation of a cost-effectiveness plane demonstrated that the results of the baseline analysis for the empirical study were robust with respect to observed PONV rates and variable costs.
- When halothane was substituted with isoflurane, propofol/isoflurane was the most effective and least costly regimen (£4.40 per patient, rate of PONV 5.7%). Propofol/isoflurane is therefore the dominant arm.
- When halothane was substituted with sevoflurane, propofol/sevoflurane was the most effective and most costly (£13.40 per patient, rate of PONV 5.7%). The ICER derived for propofol/sevoflurane compared with sevoflurane/sevoflurane is £3.10 for each PONV episode avoided.
- The use of the Dion algebraic approximation for volatile-anaesthetic use resulted in a systematic underestimation of the use of volatile agents, although the estimation of a precise inflation factor proved difficult. The impact of this inflation factor continued to result in propofol/halothane dominating the sevoflurane/sevoflurane arm.

Net benefit

Both anaesthetic regimens had an overall negative net cost, and the costs is each group were not significantly different. The net cost was negative for over 90% of patients in both study arms.

Chapter 7
Discussion

The structure and content of this discussion follows the revised Consolidated Standards for Reporting of Trials (CONSORT) statement for reporting randomised trials.[262]

The overall aim of the CESA project was to assess the relative cost-effectiveness of different anaesthetic agents in adult and paediatric day surgery. The rationale for this was a perceived need to provide the NHS with new and reliable information about the relative value for money of alternative methods of anaesthesia. The CESA project is based on the premise that that there are no differences in the long-term clinical outcomes, such as death, respiratory and cardiac sequelae or long-term cognitive differences, associated with the use of different anaesthetic agents and techniques. The optimal choice of anaesthetic agent for day-surgery anaesthesia depends on the profile of short-term, transient effects, patient preferences and the costs of the alternatives.

The CESA project comprised three interrelated studies to assess these short-term clinical, patient and cost outcomes. The first of these studies was a literature review of the clinical, patient outcome and economic literature to assess the evidence currently available. Secondly, a survey of current practice in anaesthesia for day surgery was undertaken. Both the literature review and the national survey were used to inform the design of an RCT of alternative anaesthetic agents, which was the third component of the project (CESA RCT). This chapter summarises the findings of each of these components of the CESA project. Practical problems encountered in the implementation of the CESA RCT are presented, followed by a discussion of the internal and external validity of the CESA RCT. Finally, key conclusions are drawn for health policy, clinical practice and the need for future research.

Findings of the study

Literature review

The literature review of clinical papers identified a large number of high-quality RCTs (grade I) of methods of anaesthesia and anaesthetic agents used in adult and paediatric day surgery. However, the comparability of the studies was low, owing to a wide variation in the patient groups, anaesthetic agents and treatment protocols, surgical procedures and primary clinical outcomes used. PONV was the most commonly used measure, but varied in how and when it was measured. Therefore, few firm conclusions could be drawn about the relative effectiveness of frequently used alternative agents. The review of patient-based outcomes identified mainly descriptive studies, with very few comparative evaluations. The review of the cost and economic literature yielded a small number of low-quality evaluations.

The overall findings of the literature review were that:

- the available evidence on short-term outcomes concentrated on predischarge PONV and discharge times
- there was no clinical, patient-based outcome or economic evidence to indicate the optimal agent for anaesthesia in day surgery
- there was no clinical, patient-based outcome or economic evidence to indicate the optimal method of induction (inhalational or intravenous) anaesthesia in day surgery
- TIVA is not yet standard practice in anaesthesia for day surgery in paediatric patients
- desflurane is not used in British practice and is not an appropriate comparator
- the tools used to measure outcomes were varied and mostly unvalidated
- patients may not consider PONV, mode of anaesthesia or cognitive function to be important outcomes.

National survey of anaesthetic practice for paediatric and adult day surgery

For adult day surgery, current practice is one of no premedication, a preference for induction with propofol and maintenance with isoflurane. One-tenth of respondents reported use of propofol for maintenance and one-fifth reported use of sevoflurane. A very small minority of respondents reported using desflurane. After induction, fresh gas flow rates are restricted to around 3 1/min, reflecting moderate but not ultra-low flow anaesthesia. Laryngeal masks are used in virtually all patients. Prophylactic antiemetics were used by approximately half of the

respondents. The anti-emetic of choice was ondansetron or cyclizine, for both prophylaxis and treatment. Preoperative local anaesthetics were widely used, and use varied by procedure from 51% for urological surgery to 78% in orthopaedic surgery. Bupivacaine was the most popular choice. Most respondents used intraoperative opioid analgesics (60–70% of adults). The survey indicated that almost half of all patients receive fentanyl.

For paediatric day surgery, current practice is one of no premedication, and a preference for induction with propofol (50% of respondents) or sevoflurane (25% of respondents). Maintenance of anaesthesia is via a laryngeal mask, using mainly isoflurane (45%) or sevoflurane (32%). The majority of respondents (76%) did not use a prophylactic anti-emetic and 25% always used one. The anti-emetic of choice was ondansetron, for both prophylaxis and treatment of established PONV. The majority of patients would also receive local anaesthesia (80%). Approximately half would receive intraoperative opioids and a third would receive NSAIDs preoperatively or intraoperatively.

CESA RCT

Propofol/propofol was associated with the lowest incidence of PONV and the highest cost. Propofol/isoflurane and propofol/sevoflurane were similar in the incidence of PONV. Cost was significantly increased when sevoflurane was used instead of isoflurane. Sevoflurane/sevoflurane was associated with the highest incidence of PONV and the second highest cost. The differences between sevoflurane/sevoflurane and the regimens that included propofol were statistically significant at the 1% level. There were no statistically significant differences in PONV between the groups where propofol was used for induction and a volatile agent for maintenance. The incremental cost of avoiding one episode of PONV by using propofol for both induction and maintenance was between £46.10 (compared to sevoflurane/sevoflurane) and £629.40 (compared to propofol/sevoflurane).

Using propofol for induction with a volatile agent for maintenance anaesthesia was more effective and less costly than the sevoflurane/sevoflurane regimen. The findings suggest that the use of propofol for the induction of anaesthesia is cost-effective compared to the use of sevoflurane. This finding is strengthened when patients' preferences and monetary values for the method of induction and reduced risk of PONV are incorporated in the analysis. Stated preferences tend to be greater than revealed preferences, so it is likely that the CVs given would be lower if they were reflecting revealed preferences.

Overall, all anaesthetic regimens were associated with a net benefit. The difference in net benefit between propofol/volatile agent regimens and the sevoflurane/sevoflurane regimen was statistically significant.

For the paediatric RCT, the agents were propofol/halothane and sevoflurane/sevoflurane. The incidence of PONV was statistically significantly higher with sevoflurane/sevoflurane than with propofol/halothane. In addition, sevoflurane/sevoflurane was associated with higher costs than propofol/halothane. Again this difference was statistically significant. These findings suggest that propofol/halothane is more effective and of lower cost than sevoflurane/sevoflurane.

Unlike the adult study, this finding is not confirmed by attaching monetary values to parents/guardians' preferences for method of induction and risk of PONV. There was no statistically significant difference in net benefit between sevoflurane/sevoflurane and propofol/halothane. The data indicate that parents/guardians prefer their child to have an inhalational rather than an intravenous induction. The value attached to this preference outweighs the value parents/guardians place on avoiding an episode of PONV.

Problems encountered

Literature review

The literature review was successful in identifying and assessing the current evidence in day-surgery anaesthesia, and this is summarised at the end of chapter 2. However, we were able to extract very few clear messages about optimal practice, whether effectiveness, patient acceptability, cost or efficiency was used as the basis for decisions.

National survey

No significant problems were encountered with the national survey. A high response rate was achieved (74%), similar to the rate (72%)found by Simpson and Russell,[32] providing a representative sample of the UK anaesthetist population. Minor ambiguities arose around how to answer questions on preferred adjuncts to anaesthesia, but were handled satisfactorily in the analysis.

Recruitment

The recruitment of patients was logistically demanding. Recruitment required the research

nurses to have an in-depth knowledge of the local procedures for notifying patients and parents/guardians about the forthcoming day-surgery procedure and admitting the patients on the day of surgery. The research nurses developed a standardised approach to patient recruitment for the adult and paediatric studies. The pilot study and liaison with the relevant ward and theatre staff played an important role in developing this approach to recruitment.

Generally the recruitment procedure worked well once the patient was approached, and around three-quarters of all patients approached agreed to take part. However, it was not possible to approach all patients who came in for day procedures, for a number of reasons. One particular problem was that there were not enough research nurses to recruit from all available lists. Day-patient lists may have been run in parallel and the number of study sites used meant that nurses sometimes had to be in more than one place at a time. At the time of the study, one of the trusts was undertaking a waiting-list-reduction initiative, and this led to a reduction in the numbers of paediatric patients available for recruitment.

The majority of patients received written information about the study prior to the day of their operation. However, it was not always possible to approach the patient on the morning of their operation before they were called for theatre.

The study aimed to use consultant anaesthetists who were experienced in all four anaesthetic techniques for adults and the two techniques for paediatrics. Not all consultant anaesthetists who were approached were comfortable with all the techniques, and in particular some expressed concern with using propofol TIVA. These anaesthetists were either trained to use the technique or were not recruited into the study. This limited the number of patient lists that could be used with recruited anaesthetists. In some instances, on the morning of the theatre list, a junior anaesthetist took over the place of the recruited anaesthetist and no patients could therefore be approached. Recruitment at one site was facilitated by having a research registrar anaesthetist who was dedicated to the project for 2 days per week and could take over anaesthetising the patients as required (e.g. if a non-recruited anaesthetist or a junior anaesthetist was doing the list).

Patients' willingness to participate

An appreciable number of patients (226 adults and 59 parents) refused to take part in the study because they did not want inhalational induction, either for themselves or for their children (compared with five and six, respectively, for intravenous induction). This reluctance contributed markedly to a smaller sample size than originally anticipated. However, only seven adults and two parents withdrew from the study once they were randomised to inhalational induction.

Follow-up of patients

Patients were followed up by telephone 7 days after discharge from hospital to obtain CVs and data on postdischarge resource use. It was expected that some patients would be lost to follow-up, particularly because the patient population for this study was generally healthy and working, and so often not at home. This was the situation that was commonly found. Overall, 85.3% of adults and 80.7% of parents were contacted for follow-up. There was no difference in follow-up rates between randomisation arms. This follow-up rate was facilitated by the use of research nurses for interview, who concentrated their efforts in the early evening.

Sample size

The original power calculations (using the change in the rate of PONV) required that 440 children and 1320 adults be recruited to the study. It was considered that a PONV rate of less than 20% to 10% would not be clinically significant, and the study was powered on this basis. The problems noted above meant that these recruitment targets were not achieved. However, statistically significant changes in PONV were found in both the adult and the paediatric component of the CESA RCT, indicating that the study had reached sufficient power to detect a difference in the primary outcome variable.

Adherence to protocol

The protocol was designed to reflect practice closely. This was made possible by the six anaesthetists in the project team. However, the protocol also was designed to reflect practice as defined in the literature and in the national surveys, which meant that this would not necessarily concur with local practice patterns in the clinical sites. This was expected to be an issue with the use of TIVA, sevoflurane induction and the lack of use of perioperative morphine and prophylactic antiemetics. However, in practice, with the support of the CESA research nurses, project coordinator and anaesthetists, the participating anaesthetists at both clinical sites observed the protocol conditions extremely rigorously. There were very few patients withdrawn due to protocol violations (12 children and 15 adults), a fact that supports the selection of a practice-based design for the study.

Interpretation of the CESA RCT findings

Prospective data collection using a pragmatic RCT design was chosen to evaluate the relative effectiveness, costs and cost-effectiveness of alternative anaesthetic agents. The robustness of the findings, the reliability of the data and the analysis of the CESA RCT need to be considered in the context of the clinical-trial setting and population (internal validity) and application to alternative settings and populations (external validity).

Internal validity

Although a RCT design was used to prospectively collect and analyse data, a number of factors may have affected the reliability of the results of the evaluation in the trial population and setting.

Bias

Patients were randomly allocated to treatment groups, using a computer-generated randomisation schedule. The randomisation sequence was concealed from the research nurses responsible for recruitment. The person responsible for generating the randomisation sequence was not involved in the recruitment of patients. There were no differences in the baseline demographic or clinical characteristics of the patients in the allocation groups, indicating that randomisation was successful in minimising selection and allocation bias.

It was not feasible to mask the anaesthetists, the research nurses responsible for data collection or the patients to the anaesthetic regimen to which the patient had been allocated. This may have affected the treatment given by the anaesthetists, the researcher's assessment of outcomes and the resource use or the patient's response to the anaesthetic regimen, leading to bias in the results. Available evidence suggests that such bias leads to an overestimation of the treatment effect.[262]

To reduce the impact of bias in treatment a clear treatment protocol was defined, and deviations from that protocol were monitored. Overall there were few major protocol violations that could have biased the results.

The primary outcome of PONV was recorded by recovery room or ward staff, rather than the research nurses. These staff were not blinded to treatment allocation because, to ensure continuity of care, normal practice is for recovery staff to be present during induction of anaesthesia. The measure of PONV combines a subjective assessment of the incidence of nausea with an objective assessment of vomiting. It was not possible to measure whether the patients' response to anaesthesia or their assessment of nausea was influenced by knowledge of the treatment group to which they were allocated. However, the direction of the treatment effect in favour of propofol is supported by the literature review. In addition, the overall incidence of PONV in the CESA RCT is at the low end of the range reported in the clinical trial literature.[53,68,69,74,104,108]

Precision of measures

The use of unvalidated or unpublished measures can reduce the precision of measurement and introduce bias into the results. To minimise this problem, the CESA RCT used PONV as the primary outcome. This is a widely used measure of the short-term effectiveness of alternative anaesthetic regimens. A widely used method to measure PONV was used in the CESA RCT. The cost measures and assessment of patient preferences and CV were developed specifically for the study. Both were developed according to published methods.

The patient preference and CV measures were based on a previously published study and were piloted extensively for the CESA RCT. The pilot and trial analyses of patients' preferences and the CV indicated that the majority of patients understood and were able to complete the task. However, in the adult study there was a scale effect that operated for intravenous but not inhalational induction. This means that the CV for intravenous induction may be underestimated, which would bias the analysis in favour of inhalational induction for adults. The difference in effectiveness and the net benefit in favour of intravenous induction with propofol may be higher for adults than was estimated in this study.

Two substudies of resource use were carried out as part of the CESA project to improve the precision of the cost estimates. These were a volatile anaesthetic validation study (see appendix 18) and a staff resource use time-and-motion study (see appendix 19).

The CESA RCT required accurate and detailed information on the quantities of anaesthetic used. This is more problematic with volatile anaesthetic agents because a simple measurement of volume is not possible, and vaporisers do not record this type of information. A substudy was designed to validate the Dion algebraic approximation used in most studies,[24] by obtaining the actual weight of volatile

agent used (see appendix 18). It was expected that the Dion formula would over- or underestimate the actual amount of agent used, due to differences in temperature, adsorption of the volatile, and so on, and this effect was in fact observed. It was not possible to estimate formally a 'correction factor' for the Dion formula because of the small sample size in this substudy. However, at this stage it is possible to calculate the mean difference between the Dion estimate and the true weight of volatile anaesthetic used. The actual correction of the amount of anaesthetic used ranged from 49% to 81%. The percentage mean difference was used to indicate the average magnitude of the difference between the Dion estimate and the actual weight of true anaesthetic. It is clear that the use of the Dion formula underestimates the use of volatile anaesthetic agents.

Sensitivity analysis was used to explore the impact of this imprecision on the results of the CESA RCT. Overall, the sensitivity analysis confirmed that anaesthetic regimens that used propofol for induction of anaesthesia were more cost-effective than those using sevoflurane for induction of anaesthesia. Furthermore, the slight advantage seen for propofol/isoflurane was increased when the costs of the volatile agents were inflated. This alternative was associated with net savings and a lower incidence of PONV when compared to sevoflurane/sevoflurane.

Staff resource use

The staff resource use study confirmed the stages and tasks that comprise a day-surgery episode, identified the type and grade of NHS staff present at each stage, and quantified the length of time that each grade of staff took to complete each task (see appendix 19). Differences in working practices in terms of skill mix were observed between the three hospital sites, but this did not translate into notable differences in the average semi-fixed cost. The study reported that the staff resource use of paediatric and adult patients differed, particularly on the ward postoperatively, where patient monitoring was much more intensive for children than for adults. These differences may affect the external rather than the internal validity of the results.

The assessment and recording of outcomes by the research nurses and project coordinator were subject to quality-control measures (see appendix 22). The quality-control procedures indicated a high level of consistency and reliability. These factors, taken together with the statistical and sensitivity analyses, suggest that the potential for bias or imprecision in the clinical cost and CV data recorded for the trial is low.

Precision of statistical analysis

As noted above, problems with the recruitment of anaesthetists and patients meant that the target sample size was not met. This meant that the power to detect statistically significant differences in the primary outcome may not have been sufficient. In addition, the trial was powered to test for differences in the incidence of PONV between treatment groups rather than for equivalence. These factors may mean that the absence of statistically significant differences between the three regimens that used propofol for induction of anaesthesia could be due to insufficient observations rather than to equivalence between the regimens. The published literature indicates that TIVA is associated with a lower risk of PONV than is propofol followed by a volatile anaesthetic agent. However, *post hoc* power calculations indicate that the study had 70% power to detect a difference in PONV from 20% to 10% at 1% significance.

It was not possible to control for all the factors that may affect the incidence of PONV. This, combined with the lower than optimum sample size, may have further reduced the power of the trial to detect statistically significant differences. The potential confounding variables were evenly distributed between the groups. Regression analysis was conducted to explore the impact of factors that were *a priori* thought to influence the incidence of PONV. The analysis indicated that the main determinant of PONV was anaesthetic regimen.

The CESA RCT was not powered to detect differences in the secondary outcomes of patient preferences and CV or costs. However, the analysis did indicate some statistically significant differences. Importantly, sensitivity and statistical analyses of the ICERs and net benefits confirmed the differences in PONV, costs and willingness-to-pay values between the different anaesthetic regimens.

Multiple outcomes were tested in the CESA RCT, which increases the probability that a difference will be found and shown to be statistically significant when it has in fact occurred by chance. For this reason the analysis used a low level of statistical significance (1%) to reduce the impact of multiple testing. The statistical differences found were mostly significant at less than the 1% level of significance. In addition, the key variables to be tested were defined *a priori* in a detailed

analysis plan, before the data were analysed or the randomisation codes revealed. This reduces the chance of spurious results from 'dredging' the data. The regression analysis to explore the predictors of PONV was not specified in the analysis plan. However, tests for differences and association between groups for the measure of PONV were prespecified.

External validity

The external validity, or generalisability, of the results depends on the relevance of the objectives and research questions of the CESA RCT to health-care decisions, and whether there are important differences between the patients, treatment regimens and hospital setting used for the trial and those found in routine practice.

Relevance of the CESA RCT

Evidence-based medicine is a topic under debate in all areas of clinical practice, including anaesthesia. Early reports suggested that evidence-based medicine was practised in only 10–20% of medical interventions. This claim has been refuted by clinical practitioners, and further studies have suggested that 70–95% of interventions are evidence-based.[263–265] In fact, a survey of anaesthetic practice in Australia reported that 96.7% of 159 interventions examined were evidence based.[31] However, the best evidence available for use was often of very poor quality, so clinical practitioners were having to base their clinical decision-making on grade IV evidence.

Evidence-based medicine is defined as 'medicine in which treatment decisions are based upon valid evidence supporting a treatment option that is going to be either safer, more effective or more efficient'. However, the use of the term 'evidence-based medicine' is open to interpretation. First, the quality of the evidence is important (i.e. what particular evidence practice is to be based upon), as illustrated in the study by Myles and co-workers.[31] Second, clinical-effectiveness data often provide only information on intermediate outcomes, such as clinical indicators (e.g. time to eye opening in anaesthesia). It is questionable whether statistically significant differences in these types of indicator are clinically significant. Also, the use of RCTs does not take into account practice issues, such as organisational issues and technical skills and dexterity. These factors can affect clinical outcome, patient acceptability and cost. Thus, in anaesthesia, evidence-based medicine can only be promoted if the evidence used moves beyond the use of outcome measures that do not have a clinically significant impact on the patient, reflect the importance of technical skills and dexterity in this speciality, and take into account organisational issues.

If it is proven that there are long-term differences in clinical outcomes, such as death, respiratory and cardiac sequelae or long-term cognitive differences, due to the use of different anaesthetic agents and techniques, then the choice of anaesthetic agent should incorporate consideration of these issues. In practice, the modern anaesthetic agents used in common practice have been shown to have similar long-term safety and efficacy profiles. Thus, the basis upon which to choose between agents needs to be drawn from other areas of evidence. The literature review in chapter 2 illustrates that, while anaesthetic agents have similar long-term outcomes, in the short term, there are transient differences in the side-effect profile and recovery characteristics of the patients. It is true to say that many anaesthetists select their anaesthetics on the basis of evidence about these short-term side-effect profiles and recovery characteristics. However, such a choice is only appropriate if these differences are both statistically and clinically significant in the patient group concerned. It is particularly important that evidence from inpatient anaesthesia is not applied to day surgery, due to the large difference in exposure time to the anaesthetic, the different types of surgical procedures concerned and the different patient population.

Clinical effectiveness, particularly when measured in short-term clinical indicators, should arguably not be the sole basis upon which a decision to treat should be made. Anaesthesia is a victim of its own success: in an increasingly consumerist society, patients perceive that someone must be at fault if the outcome is less than perfect. The adoption and development of day surgery is partly dependent on how day surgery compares with inpatient care in terms of effectiveness and acceptability. Patients' experiences of inpatient surgery have been studied, but it is not clear that these findings can be translated into the day-surgery setting. The literature review has provided a summary of the evidence available, although it was not clear which anaesthetic techniques are preferred by patients, and what their preferences are regarding different short-term clinical indicators. The anaesthetist's preference for a particular type of anaesthesia or their perception of patients' preferences for an intravenous induction rather than an inhalational induction may or may not coincide with that of the patient.

Furthermore, anaesthetists operate in a resource-constrained environment, and newer anaesthetic agents are invariably more costly than established agents. Therefore, the anaesthetist has to justify the use of these agents, even if they are providing improved clinical outcomes or have increased patient acceptability. The literature provided little, poor-quality economic evidence, of which very little was sufficiently robust to support policy decision-making. Lack of evidence regarding the real comparative cost of different anaesthetic techniques, and the pressure to reduce spending on drugs in NHS hospitals compounds the difficulty faced by clinical practitioners and decision-makers.

In the absence of clear guidance from the literature, clinical practitioners have little choice but to rely on their own experience and preferences, within local drug budget constraints. It is not surprising that the national survey carried out as part of the CESA project (see chapter 3) and the survey by Simpson and Russell[32] suggest that clinical practice is extremely variable in this area.

The CESA project and CESA RCT were designed in response to a call for proposals from the UK NHS R&D HTA Programme. The call for proposals was based on a perceived need for additional information about the relative effectiveness, costs and patient acceptability of alternative anaesthetic agents and techniques for day surgery to inform practice in the UK NHS. The need for this information in the UK was confirmed by the literature review and the survey of national practice, conducted as part of the CESA project. The research objectives and questions were developed to address this need.

Anaesthetic regimens and treatment protocols

The anaesthetic regimens were initially chosen to reflect practice in the UK when the trial proposal was developed in 1997. The literature review and the national survey of practice suggested that the agents, techniques and treatment protocol chosen for the adult RCT reflected current practice. However, the study did not cover all the regimens used in the UK. The agents and techniques used for the paediatric RCT were less reflective of current practice, with halothane now rarely being used for maintenance of anaesthesia. In addition, the survey indicated that prophylactic anti-emetics were routinely used in UK practice. This was expressly excluded from the treatment protocol, to increase the power of the trial to detect differences in the incidence of PONV and minimise distortion of the relative costs of the regimens.

To address these problems an extensive sensitivity analysis was undertaken to estimate the expected costs and effects if: (i) alternative anaesthetic agents, identified in the national survey, were substituted for the agents used in the paediatric CESA RCT; and (ii) prophylactic ondansetron was added to the anaesthetic regimens used in the adult CESA RCT. These analyses confirmed the results of the primary analysis that induction with propofol followed by propofol or a volatile agent for maintenance of anaesthesia is more cost-effective than induction and maintenance with sevoflurane.

Trial population

A number of factors may mean that the population of patients treated in the CESA RCT are not representative of the general population of patients receiving the day-surgery procedures used in this study. These are the eligibility criteria and willingness of patients to participate in the trial. The eligibility criteria restrict the generalisability of the results to patients undergoing the day-surgery procedures included in the CESA RCT (adult study – general, including urological surgery, orthopaedic surgery, gynaecological surgery; paediatric study – general surgery, ENT surgery), patients who do not require sedative premedication and patients who are not expected to need suxamethonium. The day-surgery procedures are commonly used and comprise a large proportion of all day surgery. The national practice survey indicates that the use of premedication and suxamethonium in routine UK practice is for less than 10% of patients. These factors would suggest that the eligibility criteria were unlikely to lead to an atypical trial population.

There was no evidence that the demographic or clinical characteristics of the patients who refused to participate in the CESA RCT differed from those who did participate. Approximately half of the patients/parents who refused to participate in the CESA RCT did not want an inhalational anaesthetic. If the patients who participated in the trial were indifferent to whether they had intravenous or inhalational induction, the willingness to pay to have an intravenous induction found in the trial may be lower than that of the population treated in routine practice. Again this would suggest that the cost-effectiveness of anaesthetic regimens which use propofol for induction is robust and applicable to the general population.

In addition, it was not possible to screen all patients who attended for day surgery to determine if they were eligible and willing to enter the trial. This meant that the sample of patients screened was not randomly drawn from the population treated. However, as discussed above, the reasons for this were logistical and there is no evidence to suggest that the patients screened were different to those not screened.

Treatment settings

The CESA RCT was conducted in two hospitals. One is a university teaching hospital NHS trust and the other a non-teaching hospital NHS trust. There was evidence of differences between the sites in terms of staffing, organisation and costs of services. However, these differences did not affect the estimates of total or variable cost. There was no evidence that the hospital was a factor that predicted the incidence of PONV. The overall unexpected admission rate was 1.2%. This and the average length of stay were lower than anticipated. There were differences between the two hospitals in the length of stay and overnight stay rates for gynaecological surgery, which probably reflected organisational differences between the sites, as the anaesthesia protocol did not differ. These factors may mean that the variable costs observed in the CESA RCT may be lower than those in other settings. Overall, this would probably tend to reduce the probability of finding a difference in the costs of the alternative anaesthetic regimens.

Chapter 8
Conclusions

The CESA project was designed to assess whether there were differences in the relative cost-effectiveness of anaesthetic regimens currently used for day surgery in the UK. The literature review and national survey indicated that:

- the anaesthetic regimens currently used were similar in long-term efficacy and safety and the choice of anaesthetic needed to be made on the basis of short-term, transient outcomes and costs
- the evidence available to inform the choice of regimen was limited
- there was variation in practice.

The CESA RCT was designed to address the relative value for money of the different anaesthetics in terms of these short-term outcomes, patient preferences and costs. A pragmatic trial design was used, which reflected the need to balance the need for data that were reliable, precise and unbiased against the practical constraints of implementing an RCT. The design and practical problems encountered meant that the internal validity of the CESA RCT was probably lower than that which would be expected from a tightly controlled explanatory trial. Inevitably, the trial could not mirror all current practice. However, an extensive sensitivity analysis indicated that the results of the primary analysis were robust and reliable.

The main conclusions drawn from the trial are as follows:

- Sevoflurane/sevoflurane is not a cost-effective regimen for day surgery in adults or children. It is associated with higher rates of PONV than propofol followed by propofol, isoflurane or sevoflurane. The cost of sevoflurane/sevoflurane is lower than that of the propofol induction regimens studied. However, the value to patients and parents of avoiding PONV is higher than any savings in resource use generated by sevoflurane/sevoflurane. This result was supported by the sensitivity analyses to test the precision of the data and choice of anaesthetic regimen and treatment protocol. Furthermore, many patients refused to take part in the study because they did not want inhalational induction, either for themselves or for their children, suggesting that this induction method is not popular among patients.
- In the adult study there were no statistically significant differences in the incidence of PONV between the regimens that used propofol for induction. However, there were statistically significant differences in the variable costs of the regimens. The propofol/isoflurane regimen was associated with the lowest cost per episode of PONV avoided and the highest net benefit when patient preferences and values were included. Again, this result was supported by the sensitivity analyses. The sensitivity analyses also suggested that propofol/isoflurane may be the most cost-effective regimen for paediatric day surgery.

Implications for clinical practice

Despite the withholding of prophylactic anti-emetics, the overall incidence of PONV is low. The national survey of anaesthetic practice suggests that the routine use of prophylactic anti-emetics is widespread. There is a case for reconsidering this practice in patients at low risk of PONV, particularly as patients and parents do not appear to place a high value on avoidance of PONV.

The national survey revealed significant intraoperative opioid use in day surgery. Opioid use was minimised in the CESA RCT, and this may have influenced the PONV rates favourably. Clinicians should explore alternative non-opioid methods of intra- and postoperative analgesia as an alternative to routine prophylactic anti-emetic use.

Decisions around clinical practice in day surgery are often extrapolated from inpatient data and outcomes. These decisions are not necessarily appropriate in the day-surgery setting.

Patients and their carers are willing to be involved in the decisions about their anaesthetic and have strong views, particularly on anaesthetic induction methods. The current development of anaesthetic preoperative information leaflets and strengthening of consent procedures should take these views into consideration.

Many adults and parents of children wish to avoid an inhalational induction. However, after receiving an inhalational induction, two-thirds of patients would be happy to receive one again.

When selecting and recommending a technique for a day patient, the anaesthetist should bear the following outcomes in mind:

- In both adults and children a sevoflurane/sevoflurane anaesthetic regimen is associated with a higher incidence of PONV than a regimen incorporating propofol. In children, sevoflurane/sevoflurane is also associated with agitation in recovery.
- In children a sevoflurane/sevoflurane regimen is more expensive than propofol/halothane or the modelled cost of propofol/isoflurane. However, the value parents place on their child receiving an inhalational induction balances out the additional cost.
- A propofol-containing regimen appears to confer anti-emetic protection. The additional anti-emetic benefit conferred by TIVA, as opposed to propofol/volatile agent, is not statistically significant. PONV aside, clinicians may also select TIVA for its 'volatile-free' environment.

Implications for future research

The CESA project identified a number of areas where further research is needed. Specific anaesthetic-related issues requiring further work are discussed below. A concern more general to the remainder of healthcare that has been highlighted by this study is the role of patients' preferences in decision-making and implications for further research in this area are also explored below.

Use of opioid analgesics

The national practice survey indicated that analgesia is provided by intraoperative opioids in 60–70% of adults, with a relatively small number receiving NSAIDs either pre- or intraoperatively. The high usage of opioids, with almost half of all patients receiving fentanyl, is perhaps surprising, given their association with nausea and vomiting. The use of NSAIDs for perioperative analgesia may, in practice, be higher than the survey suggests, for two reasons. First, the survey did not ask about the administration of postoperative analgesics, and these agents may be widely used in the postoperative period. Second, the survey instrument asked the respondent to identify just one intraoperative analgesic. Respondents may have recorded opioid usage in preference to a concurrent usage of NSAIDs.

The use of these analgesics could affect the clinical effectiveness and costs of and patient preferences for different anaesthetic regimens. This is a question that was not investigated in the CESA RCT, and further work may clarify the impact of opioid use on patient outcome after day surgery. Observational studies may prove the most useful method for identification of practice patterns.

Use of prophylactic anti-emetics

A distinction was made between prophylactic anti-emetics and those given for treatment of nausea or vomiting. Around half the respondents do not give routine anti-emetic prophylaxis to adult patients, while 30–40% always use prophylaxis, with ondansetron and cyclizine being the most popular agents. The use of prophylactic anti-emetics was lower in paediatric patients. Despite the prohibition of prophylactic anti-emetics, the overall incidence of nausea and vomiting in the CESA RCT was low. This may be because the protocol precluded the use of intraoperative morphine, although small numbers of patients received other short-acting opioids. This raises questions around the necessity for the widespread use of prophylactic anti-emetics revealed in the national survey. Systematic review of the literature around the use of these agents in day surgery may help to answer these questions.

Risks associated with PONV

The CESA RCT for adults found that an increased risk of PONV was associated with gender, with women of childbearing age being more at risk, whether undergoing gynaecological or general surgery. Higher risk was also associated with a longer anaesthetic duration, and with agitation in the recovery area. It was not within the scope of the trial to determine whether this agitation was a cause or a consequence of feeling nauseated or vomiting. Similar results have been reported in other evaluations. However, further research is required to explore the potential causes and management implications of these events, such as the clinical and economic impact of risk assessment of patients.

Other combinations of anaesthetics

The CESA RCT was not able to compare all possible combinations of anaesthetic regimens and treatment protocols currently used in routine

practice, such as the use of midazolam. Additional pragmatic research is required to explore these practice models in more detail.

Algebraic approximation of volatile anaesthetics

The substudy of volatile anaesthetic agents (see chapter 5) showed that the Dion formula consistently underestimated the quantity of volatile anaesthetic used. There were insufficient data in this substudy to create an adjusted Dion estimate. A larger primary study incorporating inpatient surgery is required to develop a formula to inform the costing of volatile anaesthetic agents.

The role of patients' preferences in decision-making

The results of the CESA RCT indicate that patient preferences and values may differ from those of anaesthetists, and that patients' values are an important component of the relative value for money of alternative anaesthetic regimens. One strategy advocated in other healthcare areas is to incorporate patient preferences and values in the clinical decision-making process. This would give the clinician additional relevant information and a structured process in which to synthesise population and individual patient information about preferences and values for the relative risks and benefits of treatment.[266–268]

However, the use of decision analytic approaches by the clinician will also be influenced by their subjective interpretation of the objective evidence and their existing subjective values, beliefs and personal experience.[266] Experience from the design of clinical trials and data collection instruments to minimise bias indicates clearly that the perceptions and values of healthcare professionals, investigators and patients are important sources of bias. This would suggest that the perceptions and values of clinicians will exert an influence on the way in which decision analysis is used, on which patients, and how the available evidence is presented and framed. These factors, combined with patients' beliefs and attitudes about illness[267] and the clinician's role, will have an impact on the patient's willingness to participate in joint decision-making, interpretation of the objective evidence and subjective assessment of the risks and benefits to them of therapy. Further research is required, therefore, to assess the feasibility and impact on patient outcomes and costs of involving patients in the decision process.

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Appendix 1

Literature search strategies

The range of databases interrogated cover relevant medical, pharmaceutical, economic, sociological, organisational and methodological evidence. The following databases were searched up to December 2000:

- MEDLINE
- NHS Centre for Reviews and Dissemination DARE database
- Bath Information and Dissemination Service (BIDS)
- CINAHL database
- Cochrane Library
- EMBASE
- PsycINFO
- EconLit
- HEED
- NHS EED.

There were four stages to the review process:

- To identify potentially appropriate studies from the literature database using an inclusive search strategy.
- To identify manually all comparative studies on anaesthesia in adult and paediatric day surgery using one of the following agents: N_2O, propofol, thiopentone, halothane, enflurane, isoflurane, sevoflurane.
- To obtain references and re-screen to exclude any studies that were not comparative studies on anaesthetic techniques relating to day surgery. No restrictions on types of outcome measured were made. Studies that contained information relevant to more than one review section were included in the relevant reviews. The economic literature search identified very few studies, and so was expanded to include non-comparative studies.
- To circulate studies to reviewers, where further exclusions may be required.

The EMBASE searches shown below were modified for use in other reference databases.

Clinical outcomes literature

Search history (number of records in parentheses):

1. anesth* or anaesth* (112,349 records)
2. day surgery (569 records)
3. day case surgery (258 records)
4. outpatient surgery (300 records)
5. ambulatory surgery (1725 records)
6. strabismus surgery (870 records)
7. #2 or #3 or #4 or #5 or #6 (3094 records)
8. #1 and #7 (1540 records)
9. su=human (2,244,359 records)
10. dt=review (24,3057 records)
11. dt=letter (15,7902 records)
12. dt=editorial (54,146 records)
13. #8 and #9 (1434 records)
14. #13 not (#12 or #11 or #10) (1162 records)
15. propofol or thiopentone or halothane (13,068 records)
16. isoflurane or enflurane or sevoflurane or nitrous oxide (12,313 records)
17. #15 or #16 (20,227 records)
18. #14 and #17 (395 records)

Patient-based outcomes literature

1. anesth* or anaesth* (88,179 records)
2. pt=editorial (54,322 records)
3. pt=letter (179,921 records)
4. tg=human (218,9306 records)
5. propofol (3071 records)
6. enflurane or halothane or sevoflurane or isoflurane (7238 records)
7. nitrous oxide or thiopentone (3745 records)
8. 'quality-adjusted life years' (114 records)
9. utilit* (14,153 records)
10. willingness to pay (96 records)
11. QALY (166 records)
12. OUTCOME (132,748 records)
13. quality of life (18,088 records)
14. nausea (8308 records)
15. vomiting (9759 records)
16. pain (69,605 records)
17. #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 (228,399 records)
18. #17 and #1 (13,818 records)
19. #17 and #4 (213,788 records)
20. #18 and #4 (11,950 records)
21. #20 and (#6 or #7) (709 records)
22. #21 not (#2 or #3) (694 records)
23. day and surgery (18,185 records)
24. day and case and surgery (2560 records)

25. ambulatory surgery (559 records)
26. outpatient surgery (264 records)
27. day surgery (525 records)
28. day case surgery (204 records)
29. #25 or #26 or #27 or #28 (1353 records)
30. #29 and #22 (51 records)

Economic literature

1. anesth* or anaesth* (88,179 records)
2. 'costs and cost analysis' (6549 records)
3. 'cost benefit analysis' (10,026 records)
4. cost benefit analysis (10,026 records)
5. economic evaluation (499 records)
6. economic analysis (310 records)
7. cost effectiveness (4229 records)
8. hospital costs (1553 records)
9. health resources (1743 records)
10. pt=editorial (54,322 records)
11. pt=letter (179,921 records)
12. tg=human (2,189,306 records)
13. propofol (3071 records)
14. enflurane or halothane or sevoflurane or isoflurane (7238 records)
15. nitrous oxide or thiopentone (3745 records)
16. economics (49,923 records)
17. cost of illness (1468 records)
18. cost saving or cost minimisation or cost minimization (505 records)
19. cost benefit (10,583 records)
20. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #16 or #17 or #18 or #19 (56,223 records)
21. #1 and #12 and #20 (1170 records)
22. #21 and (#13 or #14 or #15) (103 records)
23. #22 (103 records)
24. #22 and (py=1997–1999) (42 records)

Further searches

First search strategy

Two further literature searches were carried out on all the databases, with the assistance of Lee Hooper (Research Associate in Evidence Based Care and Systematic Review, The Cochrane Suite, MANDEC University Dental Hospital of Manchester, UK) to identify any further studies.

Search period 1997 to November Week 4 2000; saved citations 1–80 from set 29:

1. anaesth$.mp. [mp=title, abstract, registry number word, mesh subject heading] (7984 records)
2. anesth$.mp. [mp=title, abstract, registry number word, mesh subject heading] (26,432 records)
3. 1 or 2 (30,180 records)
4. halothane.mp. [mp=title, abstract, registry number word, mesh subject heading] (1389 records)
5. enflurane.mp. [mp=title, abstract, registry number word, mesh subject heading] (235 records)
6. sevoflurane.mp. [mp=title, abstract, registry number word, mesh subject heading] (850 records)
7. isoflurane.mp. [mp=title, abstract, registry number word, mesh subject heading] (1548 records)
8. propofol.mp. [mp=title, abstract, registry number word, mesh subject heading] (1909 records)
9. nitrous oxide.mp. [mp=title, abstract, registry number word, mesh subject heading] (1279 records)
10. 4 or 5 or 6 or 7 or 8 or 9 (5195 records)
11. 3 and 10 (4669 records)
12. limit 11 to (human and english language) (2472 records)
13. nause$.mp. [mp=title, abstract, registry number word, mesh subject heading] (4380 records)
14. vomit$.mp. [mp=title, abstract, registry number word, mesh subject heading] (4988 records)
15. post-operative.mp. [mp=title, abstract, registry number word, mesh subject heading] (2734 records)
16. dizz$.mp. [mp=title, abstract, registry number word, mesh subject heading] (1207 records)
17. readmi$.mp. [mp=title, abstract, registry number word, mesh subject heading] (1153 records)
18. cost$.mp. [mp=title, abstract, registry number word, mesh subject heading] (33,086 records)
19. econom$.mp. [mp=title, abstract, registry number word, mesh subject heading] (11,140 records)
20. resour$.mp. [mp=title, abstract, registry number word, mesh subject heading] (9920 records)
21. quality of life.mp. [mp=title, abstract, registry number word, mesh subject heading] (12,910 records)
22. utility.mp. [mp=title, abstract, registry number word, mesh subject heading] (8686 records)
23. utilit$.mp. [mp=title, abstract, registry number word, mesh subject heading] (8889 records)

24. preferen$.mp. [mp=title, abstract, registry number word, mesh subject heading] (16,415 records)
25. satis$.mp. [mp=title, abstract, registry number word, mesh subject heading] (15,974 records)
26. length of stay.mp. [mp=title, abstract, registry number word, mesh subject heading] (6158 records)
27. 13 or 14 or15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (108,081 records)
28. 12 and 27 (396 records)
29. limit 28 to (human and english language) (396 records)
30. from 29 keep (80 records)

Second search strategy

1. explode "Anesthesia"/ all subheadings (1297 records)
2. (anesth* or anaesth*) in TI, TO, AB (3082 records)
3. "Propofol"/ all subheadings (191 records)
4. "Nitrous oxide"/ all subheadings (97 records)
5. "Enflurane"/ all subheadings (10 records)
6. "Halothane"/ all subheadings (81 records)
7. "Isoflurane" / all subheadings (108 records)
8. (enfluran* or halothan* or isofluran* or propofol* or sevefluran*) in TI, TO, AB (499 records)
9. nitrous* next oxide* (151 records)
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 (3549 records)
11. "Surgery"/ all subheadings (273 records)
12. explode "Surgical-Procedures-Operative"/ all subheadings (21,163 records)
13. (surgery* or surgical*) in TI, TO, AB (12,385 records)
14. #11 or #12 or #13 (26,845 records)
15. #10 and #14 (1550 records)
16. explode "Economics"/ all subheadings (3674 records)
17. (cost* next saving*) or cost next minimi*ation* or (cost* next benefit*) (990 records)
18. cost* near illness* (211 records)
19. economicI (3758 records)
20. health* next resource* (187 records)
21. hospital* next cost* (204 records)
22. (cost* next hospital*) or (cost* next effective*) (1016 records)
23. cost* near (benefit* and analys*) (854 records)
24. (#17 or #18 or #19 or #20 or #21 or #22 or #23) in TI, TO, AB, MESH (4512 records)
25. #16 or #24 (5770 records)
26. "Pain-Measurement"/ all subheadings (673 records)
27. explode "Postoperative-Complications"/ all subheadings (4053 records)
28. pain* (5527 records)
29. vomit* (626 records)
30. nause* (552 records)
31. quality* next life* (1774 records)
32. QALY (26 records)
33. quality* near (adjust* and year*) (113 records)
34. contingent* next value* (5 records)
35. cognitive* next failure* (4 records)
36. PHBQ (0 records)
37. POMS (20 records)
38. post*hospital next behav* (0 records)
39. profile* near mood* (30 records)
40. explode "Quality of Life"/ all subheadings (1208 records)
41. "Quality-Adjusted-Life-Years" in MIME, MJME (79 records)
42. (#28 or #29 or #30 or # 31 or # 32 or # 33 #34 or #35 or #36 or #37 or #38 or #39) in TI, TO, AB, MESH, MJME, MIME (7525 records)
43. #26 or #27 or #40 or #41 or #42 (10,916 records)
44. #25 or #43 (16,179 records)
45. #15 and #44 (490 records)
46. (TG=animal) not (TG=human) and (TG=animal) (36,579 records)
47. #45 not #46 (452 records)
48. PT=letter (9916 records)
49. PT=editorial (3780 records)
50. #48 or #49 (13,695 records)
51. #47 not #50 (442 records)

Appendix 2

Meta-analyses of adult clinical outcomes studies

TABLE 65 *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Authors' conclusions	Reviewers' comments, grade of evidence
Dexter and Tinker, 1995,[40] USA	Study included inpatient surgery Desflurane vs propofol: 6 studies (229 patients) Desflurane vs isoflurane: 8 studies (316 patients) N_2O in all studies except one	Time to discharge (minutes)	Propofol vs desflurane: 17 min difference (95% CI, 4 to 30) Isoflurane vs desflurane: no difference found No other results included	There are only minor clinically important differences between desflurane and isoflurane or propofol with respect to time to discharge	MEDLINE only searched from 1966 to November 1994. No studies were blinded. Random-effects meta-analysis used. Not clear that only ambulatory studies were included
Divatia *et al.*, 1996,[41] USA	Study included inpatient surgery N_2O vs no N_2O: 24 studies	PONV	PONV: no N_2O was better than N_2O (OR = 0.63; 95% CI, 0.53 to 0.75; $p < 0.0001$)	Omission of N_2O results in a risk reduction of PONV by 28%	MEDLINE only searched from 1966 to December 1994. Fixed-effects meta-analysis (test for heterogeneity was negative)
Ebert *et al.*, 1998,[42] USA	Study included inpatient surgery Sevoflurane vs propofol: 8 studies (2008 patients) Sevoflurane vs propofol: 3 day surgery studies (400 patients) Sevoflurane vs isoflurane: 3 studies (436 patients) Not clear what adjunctive anaesthesia was used	Eligibility for PACU discharge, difference (minutes): sevoflurane/isoflurane; sevoflurane/propofol PONV: sevoflurane/isoflurane; sevoflurane/propofol	Discharge time difference: sevoflurane/isoflurane, –1.7 (95% CI, –5.6 to 2.3); sevoflurane/propofol, –3.6 (95% CI, –12.6 to 5.3) PONV: sevoflurane/isoflurane, 51/50 (NS); sevoflurane/propofol, 48/40 (NS)	Times to early recovery were significantly shorter for sevoflurane over isoflurane, but the same for sevoflurane vs propofol. Post-anaesthesia recovery times were similar	Clinical database from Abbott Laboratories on FDA phase II and III completed trials. No studies were blinded. Random-effects meta-analysis used. Not clear that only ambulatory studies were included; the range of lengths of anaesthesia suggests that inpatient surgery was included
Joo and Perks, 2000,[43] Canada	Study included inpatient surgery Propofol induction vs sevoflurane/N_2O induction: 12 studies	Intubation events PONV (7 studies, 692 patients)	PONV: propofol TIVA better than sevoflurane (OR = 4.24; 95% CI, 1.90 to 9.47; $p < 0.05$)	PONV was almost twice as common in the sevoflurane group	MEDLINE, EMBASE and the Cochrane Library were searched from 1992 to 1999, plus handsearching. Random-effects meta-analysis done

continued

***TABLE 65* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Authors' conclusions	Reviewers' comments, grade of evidence
McQuay and Moore,1998,[44] England	Propofol vs other anaesthetics for induction Propofol vs other anaesthetics for maintenance TIVA vs other anaesthetics N_2O vs no N_2O 215 studies (31,801 patients)	PONV: complete emetic control; nausea; early vomiting (up to 6 h); late vomiting (up to 48 h)	Results only presented graphically < 5 NNT for: reduction of nausea by use of propofol maintenance	None regarding this specific issue	Results difficult to interpret or use due to typographical errors. Not clear what the comparators were
Sneyd *et al.*, 1998,[45] England	Study included inpatient surgery Propofol compared with inhalational agents for maintenance: 96 studies	PONV in adults and children compared with isoflurane, sevoflurane Effect of opiates and N_2O	OR = 0.267 (95% CI, 0.220 to 0.325); 3.7-fold reduction in risk of PONV with propofol	Propofol maintenance: associated with low PONV Induction agent: no effect Choice of inhalational agent: no effect N_2O: no effect Opiate: no effect	MEDLEY database (proprietary database owned by Zeneca). Method of meta-analysis not reported
Tramer *et al.*, 1996,[46] England	Study included inpatient surgery Meta-analysis of PONV and N_2O: 24 studies (2478 patients)	PONV: complete emetic control; nausea; early vomiting (up to 6 h); late vomiting (up to 48 h)	Complete emetic control: no significant change Complete nausea: no significant change Early vomiting: NNT = 11.8 (95% CI, 8.5 to 19.4) Late vomiting: NNT = 13.8 (95% CI, 8.8 to 31.6)	Omitting N_2O from general anaesthesia decreases PONV if the baseline risk of vomiting is high	MEDLINE only searched from 1966 to May 1995. Method of meta-analysis not reported
Tramer *et al.*, 1997a,[47] England	Study included inpatient surgery Meta-analysis of PONV and propofol anaesthesia: 84 studies (3098 patients)	PONV: complete emetic control; nausea; early vomiting (up to 6 h); late vomiting (up to 48 h)	Propofol for induction: any event, NNT = 20.9 (95% CI, 8.3 to ∞) Propofol for maintenance: any event, NNT = 6.2 (95% CI, 4.7 to 9)	Propofol may have a clinically relevant effect on PONV, but only in the short term, when given as a maintenance regimen and the baseline PONV rate without prophylaxis is > 20%	MEDLINE only searched from 1966 to December 1995. Method of meta-analysis not reported
Tramer *et al.*, 1997b,[48] England	Study included inpatient surgery Meta-analysis of PONV and propofol + N_2O vs propofol with no N_2O	PONV: complete emetic control; nausea; early vomiting (up to 6 h); late vomiting (up to 48 h)	NNT (95% CI) results from Tramer *et al.* 1996 and 1997b	Omitting N_2O was as good as using propofol for maintenance at reducing PONV rates	MEDLINE only searched from 1966 to December 1995. Method of meta-analysis not reported

FDA, Food and Drugs Administration (USA); NNT, numbers needed to treat; PACU, postanaesthesia care unit

Appendix 3

Quality criteria for published studies

Hierarchy of evidence

Grade I: properly randomised controlled trial.
Grade II-1a: well-designed controlled trial with pseudo-randomisation. ('Pseudo-randomisation' refers to alternate allocation, allocation by birth date or case-note number.)
Grade II-1b: well-designed controlled trial without randomisation.
Grade II-2a: well-designed cohort prospective study with concurrent controls.
Grade II-2b: well-designed cohort prospective study with historical controls.
Grade II-2c: well-designed cohort retrospective study with concurrent controls.
Grade II-3: well-designed case–control retrospective study.
Grade III: large differences from comparisons between time and/or places with and without intervention (in some circumstances these may be equivalent to grade I or II).
Grade IV: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Study design checklist for assessing validity

RCTs

1. Was the assignment to the treatment groups really random?
2. Was relatively complete follow-up achieved?
3. Were the outcomes of people who withdrew described and included in the analysis?
4. Were those assessing outcomes blind to the treatment allocation?
5. Were the control and treatment groups comparable at entry?
6. Were groups treated identically other than for the named intervention?

Cohort studies

1. Are the exposed people representative of the standard users of the intervention?
2. Was the non-exposed cohort selected from the same population as the exposed cohort?
3. What confounding factors may affect the outcome?
4. Were these confounding factors controlled for?
5. Was the outcome assessment blind to exposure status?
6. Was an adequate proportion of the cohort followed up?

Case–control studies

1. Was the disease state of the cases reliably assessed?
2. Was there a potential for selection bias?
3. Were controls selected from a similar population as the cases?
4. Were hazards and interventions assessed in the same way for cases and controls?
5. Was follow-up long enough?

Longitudinal surveys or case series

1. Is the study based on a random sample selected from a suitable sampling frame?
2. Is there any evidence that the sample is representative of standard users of the intervention?
3. Are the inclusion criteria clearly defined?
4. Was follow-up long enough?
5. Were outcomes assessed objectively?

Quality assessment of patient-based outcome studies[49]

Outcome measures for clinical trials should be chosen by evaluating evidence about instruments in relation to the following eight criteria.

- Appropriateness: is the content of the instrument appropriate to the questions which the clinical trial is intended to address?
- Reliability: does the instrument produce results that are reproducible and internally consistent?
- Validity: does the instrument measure what it claims to measure?
- Responsiveness: does the instrument detect changes over time that matter to patients?
- Precision: how precise are the scores of the instrument?
- Interpretability: how interpretable are the scores of an instrument?
- Acceptability: is the instrument acceptable to patients?
- Feasibility: is the instrument easy to administer and process?

Quality assessment of cost and economic studies

The papers were reviewed for quality of (i) the source and methods of data collection and (ii) prespecified criteria for reliable and comprehensive economic evaluations.[50] Studies that were not defined as full economic evaluations by the author were not assessed on all categories of the criteria. Papers were graded for six categories of economic criteria, as follows.

- Study design:
  (a) Good = meets criteria 1–7, 20 and 21
  (b) Adequate = meets criteria 1, 3, 5, 6 and 20
  (c) Inadequate = does not meet one or more of criteria 1, 3, 5, 6 and 20.
- Effectiveness data:
  (a) Good = meets criteria 8–11.
  (b) Adequate = meets criteria 8 and 11.
  (c) Inadequate = does not meet one or more of criteria 8 and 11.
- Outcome data:
  (a) Good = meets criteria 12–15.
  (b) Adequate = meets criteria 12 and 14.
  (c) Inadequate = does not meet one or more of criteria 12 and 14.
- Cost data:
  (a) Acceptable = meets criteria 16–19.
  (b) Unacceptable = does not meet one or more of criteria 16–19.
- Analysis:
  (a) Good = meets criteria 22–35.
  (b) Adequate = meets criteria 22, 23, 26, 27, 29, 30 and 31.
  (c) Inadequate = does not meet one or more of criteria 22, 23, 26, 27, 29, 30 and 31.

Appendix 4

Adult clinical outcomes studies

TABLE 66 *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Alhashemi *et al.*, 1997,[29] Canada RCT	(1) Thiopentone, fentanyl/isoflurane, N_2O (n = 31) (2) Propofol, alfentanil/N_2O, alfentanil (n = 31) (3) Propofol, alfentanil/TIVA, alfentanil–suxamethonium/alcuronium (n = 31) N_2O: given in group (a) Premedication: midazolam Procedures: knee surgery Gender: 60% men Mean ± SD age: 37.4 ± 11 years	(a) Open eyes (b) Verbal commands (c) Aldrete score (d) Subjective scale (e) Trieger Dot Test (f) PONV	(a): (1) 8.5, (2) 2.2, (3) 8.8 min; $p < 0.0001$ (b): (1) 8.9, (2) 3.0, (3) 9.2 min; $p < 0.0001$ (c): (1) 100, (2) 96, (3) 92; NS (d) NS (e) NS (f): (1) 23%, (2) 48%, (3) 16%; $p < 0.02$	Grade I Method of randomisation not reported Double-blind Group (b) cannot be included, as not standard technique Other groups too dissimilar to include in the analysis
Apfelbaum *et al.*, 1996,[51] USA RCT	(1) Propofol, desflurane no N_2O (n = 5) (2) Propofol, desflurane, N_2O (n = 5) (3) Propofol TIVA, N_2O (n = 5) (4) Desflurane, desflurane, no N_2O (n = 5) N_2O: given Premedication: none Gender: men Age: 18–39 years	(a) Open eyes (b) Obey commands (c) Give date of birth (d) Orientated (e) Sit/stand/walk (f) Discharge (g) Maddox Wing (h) Auditory reaction time (i) Visual reaction time (j) Co-ordination (k) DSST (l) Word recall	(a): (1) 10, (2) 6, (3) 15, (4) 8 min (b): (1) 10, (2) 6, (3) 15, (4) 8 min (c): (1) 13, (2) 7, (3) 18, (4) 10 min (d): (1) 14, (2) 8, (3) 19, (4) 10 min (e): (1) 34, (2) 26, (3) 33, (4) 27 min (f): (1) 126, (2) 81, (3) 70, (4) 106 min (g): (1) 2, (2) 2, (3) 5, (4) 2 (h): (1) 10, (2) 40, (3) 40, (4) 20 min (i): (1) 10, (2) 10, (3) 40, (4) 20 min (j): (1) 3, (2) 2, (3) 8, (4) 0 (k): (1) –2, (2) –5, (3) –8, (4) –1 (l): (1) 3, (2) 3, (3) 3, (4) 3 s Results all at 1 h Group 3 significantly slowest; $p < 0.01$ Group 4 significantly fastest; $p < 0.01$ No difference after 1 h	Grade II–1b Blind Crossover Volunteers

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Arellano *et al.*, 2000,[52] Canada Multicentre RCT	(1) Propofol TIVA, no N_2O (n = 750) (2) Propofol TIVA, N_2O (n = 750) N_2O: given in group 2 Premedication: none Procedures: (X) termination of pregnancy; (Y) laparoscopy	(a) Time to street-fit (b) PONV	(a) (X): (1) 113, (2) 110 min; NS (a) (Y): (1) 167, (2) 167 min; NS (b) NS difference	Grade I Method of randomisation: sealed envelopes Blind
Ashworth and Smith, 1998,[53] UK RCT	(1) Propofol, isoflurane, N_2O (n = 30) (2) Propofol TIVA, N_2O (n = 30) (3) Propofol, desflurane, N_2O (n = 30) N_2O: given Premedication: none Procedures: mixed body surface surgery Age: 18–70 years	(a) Open eyes (b) Obey commands (c) Orientation (d) Sit unaided (e) Discharge (f) PONV (% with no PONV)	(a): (1) 5.1, (2) 5.6, (3) 4.4 min; NS (b): (1) 5.9, (2) 6.6, (3) 5.1 min; NS (c): (1) 6.5, (2) 7.2, (3) 5.4 min; NS (d): (1) 45, (2) 31, (3) 33 min; NS (e): (1) 157, (2) 156, (3) 166 min; NS (f): (1) 93%, (2) 90%, (3) 100%; NS	Grade I Method of randomisation not reported Blind
Bernstein *et al.*, 1989,[54] Sweden RCT	(1) Methohexitone, alfentanil 7 µg/kg (n = 29); methohexitone TIVA, no N_2O (2) Methohexitone, alfentanil 15 µg/kg (n = 30); ethohexitone TIVA, no N_2O (3) Thiopentone TIVA, N_2O (n = 30) N_2O: given in group 3 Premedication: none Procedures: D&C Gender: women Age: 16–74 years	(a) Open eyes (b) Orientation (c) PONV	(a): (1) 9.3, (2) 8.3, (3) 14.8 min; $p < 0.01$ (b): (1) 10.9, (2) 9.2, (3) 16.7 min; $p < 0.001$ (c): (1) 6.9%, (2) 20%, (3) 16.7%; NS	Grade I Method of randomisation not reported Not blind
Biswas and Hatch, 1989,[55] Australia RCT	(1) Thiopentone, halothane, N_2O (n = 26) (2) Thiopentone, enflurane, N_2O (n = 25) (3) Thiopentone, alfentanil, N_2O (n = 26) N_2O: given Premedication: none Procedures: cystoscopy Gender: not reported Age: 15–85 years	(a) Open eyes (b) Obey command (c) Orientation (d) Trieger Dot Test	(a): (1) 8.6, (2) 5.2, (3) 2.0 min; $p < 0.0005$ (b): (1) 10.2, (2) 6.4, (3) 4.9 min; $p < 0.0005$ (c): (1) 10.4, (2) 7.3, (3) 6.2 min; $p < 0.004$ (d): Large variability; no valid conclusions possible	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Cade *et al*, 1991,[56] Australia RCT	(1) Propofol TIVA, N_2O (n = 35) (2) Methohexitone TIVA, N_2O (n = 35) N_2O: given Premedication: none Analgesia: fentanyl 1 µg/kg Procedures: gynaecological procedures < 30 min long Gender: women Age: < 30 years	(a) Respond to voice (b) Awaken (c) Orientation (d) Discharge (e) Ambulation (f) PONV	(a) Shorter; $p < 0.02$ (b) No difference (c) No difference (d) No difference (e) Shorter; $p < 0.05$ (f) Group1 less than group 2; $p < 0.04$	Grade I Method of randomisation not reported Raw data not given, only results of analysis
Carroll *et al*., 1997,[57] UK RCT	(1) Alfentanil, propofol LMA, desflurane, N_2O (n = 20) (2) Alfentanil, propofol LMA, propofol TIVA, N_2O (n = 20) N_2O: given Premedication: none Procedures: not reported Gender: 30% women Age: > 50 years	(a) Open eyes (b) Obey commands (c) Date of birth (d) Simple reaction time (e) Peg board (f) Word retention (g) PONV (h) Street-fit	(a): (1) 6.7, (2) 8.7 min; NS (b): (1) 7.3, (2) 9.7 min; NS (c): (1) 10.8 min; NS (d): NS (e): NS (f): NS (g): NS (h): (1) 92.7, (2) 111.9 min; NS	Grade I Method of randomisation not reported Not blind
Carter *et al*., 1985,[58] UK RCT	(1) Halothane (n = 20) (2) Enflurane (n = 20) (3) Isoflurane (n = 20) N_2O: given Premedication: none Procedures; D&C Gender: women Age: 20–50 years	(a) Time to open eyes (b) Time to give date of birth (c) Post-box test (d) P-deletion test	(a): (1) 5.5, (2) 5.1, (3) 6.2 min; NS (b): (1) 6.4, (2) 5.8, (3) 7.4 min; $p < 0.05$ for groups (b) and (c) (c): (1) 34.2, (2) 33.8, (3) 40.2; NS (d): Errors preanaesthesia (1) 7.8, (2) 5.4, (3) 4.9; errors postanaesthesia (1) 6.9, (2) 9.0, (3) 6.8; $p < 0.05$ group (b) (d): Lines completed preanaesthesia (1) 25.2, (2) 26.4, (3) 23.5; lines completed post-anaesthesia (1) 24.5, (2) 26.4, (3) 26.3; $p < 0.05$ group (c)	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Cartwright *et al.*, 1997,[59] UK Multicentre RCT	(1) Propofol, isoflurane, remifentanil (n = 102) (2) Propofol, isoflurane, alfentanil (n = 99) N_2O: none Premedication: none IPPV: vecuronium Procedures; mixed Gender: 50% women Age: 18–65 years	(a) Response to verbal stimulation (b) Learning memory (c) Discharge (d) Trieger Dot Test (e) DSST (f) PONV	(a): (1) 9, (2) 7 min; NS (b): (1) 13, (2) 14; NS (c): (1) 206, (2) 210 min; NS (d): Remifentanil better than alfentanil; $p < 0.05$ (no data given) (e): Remifentanil better than alfentanil; $p < 0.05$ 30 min: (1) 33, (2) 38 60 min: (1) 44, (2) 47 90 min: (1) 45, (2) 48 (f): (1) 25, (2) 27 patients; NS	Grade I Method of randomisation not reported Double-blind
Cheng *et al.*, 1999,[60] Taiwan RCT	(1) Propofol, propofol TIVA, ketamine spontaneous ventilation (n = 30) (2) Thiopentone, fentanyl, atracurium, isoflurane, IPPV (n = 30) N_2O: none Premedication: atropine + prochlorperazine Procedures: gynaecological laparoscopy Gender: women Age: 17–48 years	(a) Open eyes (b) Obey commands (c) P-deletion test (d) PONV (e) Sore throat NB: group (a) not intubated	(a): NS (b): NS (c): NS (d): (1) 7%, (2) 30%; $p < 0.05$ (e): (1) 7%, (2) 41%; $p < 0.001$	Grade I Method of randomisation not reported Not blind
Chittleborough *et al.*, 1992,[61] Australia RCT	(1) Thiopentone, enflurane, N_2O (n = 20) (2) Propofol, enflurane, N_2O (n = 20) Analgesia: fentanyl Muscle relaxant: vecuronium N_2O: given Premedication: none Procedures: oral surgery Gender: 60% women Mean ± SD age: 21.4 ± 3.4 years	(a) Sit unaided (b) Discharge (c) P-deletion test (d) Flashing lights (e) PONV	(a): (1) 59.7, (2) 44.8 min; $p < 0.05$ (b): (1) 133.5, (2) 113.1 min; $p < 0.05$ (c, d): No differences (e): No differences	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Chung *et al.*, 2000,[62] UK Multinational, multicentre trial, random 70 centres over 14 countries (Glaxo sponsored)	Remifentanil infusion Propofol induction (1) Isoflurane (n = 285) (2) Enflurane (n = 285) (3) Propofol TIVA (n = 284) N_2O: none Premedication: none Procedures: mixed Gender: 63% men Age: 18–78 years	(a) Time to extubation (b) Respond to command (c) Aldrete score (d) Time to discharge from recovery (e) PONV	(a) NS (b): (1) 6, (2) 6, (3) 7 min; $p < 0.05$ (c) NS (d) NS (e) NS	Grade I Method of randomisation: computer-generated random numbers Not blind
Collins *et al.*, 1996,[63] UK RCT	(1) Propofol TIVA, alfentanil (n = 15) (2) Propofol/isoflurane (n = 15) N_2O: in group (b) only Premedication: none Procedures: laparoscopic sterilisation Gender: women Age: 25–39 years	(a) Nausea on a VAS (b) Pain on a VAS (c) Drowsiness on a VAS (d) P-deletion test (e) Time to opening eyes (f) Time to give date of birth	(a): (1) 2, (2) 17 at 1 h ($p < 0.01$); (1) 2, (2) 10 at 2 h ($p < 0.01$) (b): (1) 48, (2) 45 at 1 h (NS); (1) 35, (2) 45 at 2 h (NS) (c): (1) 47, (2) 55 at 1 h (NS); (1) 27, (2) 30 at 2 h (NS) (d): (1) 158, (2) 164 preoperatively (NS); (1) 131, (2) 115 at 1 h ($p < 0.01$) (e): (1) 9.3, (2) 8.4 min; NS (f): (1) 13.6, (2) 12.9; NS	Grade I Method of randomisation not reported Blind
Dashfield *et al.*, 1998,[64] England RCT	(1) Propofol, sevoflurane, N_2O (n = 20) (2) Sevoflurane, sevoflurane, N_2O (n = 20) N_2O: given Premedication: none Procedures: knee arthroscopy Gender: 20% women Mean ± SD age: 40 ± 10 years	(a) Open eyes (b) Computerised coordination test (c) P-deletion test (d) PONV at 90 min	(a): (1) 381, (2) 508 s (b): No differences (c): No differences (d): (1) 0, (2) 0 No difference between groups	Grade I Method of randomisation: computer-generated random numbers Not blind
De Grood *et al.*, 1987,[65] The Netherlands RCT	(1) Propofol TIVA (n = 15) (2) Etomidate TIVA (n = 15) (3) Propofol, N_2O, isoflurane (n = 15) (4) Etomidate, N_2O, isoflurane (n = 15) (5) Thiopentone, N_2O, isoflurane (n = 15) N_2O: in groups 3–5 Premedication: none Procedures: gynaecological laparoscopy	(a) Open eyes (b) Answer questions	(1): (a) 7.9, (b) 8.6 min (2): (a) 13.8, (b) 19.3 min (3): (a) 9.7, (b) 11.3 min (4): (a) 12.9, (b) 15.5 min (5): (a) 15.8, (b) 18.0 min No significant differences	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Djaiani *et al.*, 1999,[67] Wales RCT	(1) Saline, propofol, isoflurane, N_2O (n = 18) (2) Propofol, propofol, isoflurane, N_2O (n = 18) (3) Midazolam, propofol, isoflurane, N_2O (n = 18) N_2O: given Premedication: none Procedures: minor orthopaedic surgery Gender: 4% women Mean ± SD age: 40 ± 13 years	(a) Open eyes (b) Time to discharge	(a): No differences (no data given) (b): (1) 122, (2) 123, (3) 152 min; $p < 0.001$. Group 3 slower than either 1 or 2 (no data given)	Grade I Method of randomisation not reported Double-blind
Ding *et al.*, 1993,[66] USA RCT	(1) Thiopentone/enflurane (n = 23) (2) Propofol/enflurane (n = 17) (3) Propofol TIVA (n = 21)	(a) Time to open eyes (b) Time to sit in chair (c) Tolerate fluids (d) Walk to bathroom (e) Fit for discharge (f) Pain (g) PONV	(a): (1) 6.1, (2) 4.6, (3) 3.5 min; $p < 0.05$ for (c) (b): (1) 84, (2) 86, (3) 90 min; NS (c): (1) 89, (2) 92, (3) 110 min; NS (d): (1) 142, (2) 170 min; NS (e): (1) 169, (2) 185 min; NS (f): (1) 39, (2) 41, (3) 38; NS (g): (1) 43%, (2) 41%, (3) 24%; $p < 0.05$ No difference in post-operative VAS scores for sedation, anxiety or pain	Grade I Method of randomisation not reported Single blind
Eriksson *et al.*, 1995,[68] Finland RCT	(1) Propofol, sevoflurane (n = 25) (2) Propofol, isoflurane (n = 25) N_2O: given Premedication: none Analgesia: fentanyl Muscle relaxant: vecuronium Procedures: gynaecological laparoscopy Mean ± SD age: 32.5 ± 5 years	(a) Open eyes (b) Obey commands (c) Orientation (d) Sit unaided (e) Walk (f) Discharge (g) DSST (h) PONV in PACU (i) PONV in first 24 h	(a): (1) 2.3, (2) 4.1 min; $p < 0.05$ (b): (1) 2.6, (2) 4.3 min; $p < 0.05$ (c): (1) 2.8, (2) 4.7 min; $p < 0.05$ (d): (1) 33, (2) 34 min; NS (e): (1) 72, (2) 66 min; NS (f): (1) 281, (2) 242 min; NS (g): No differences (h): (1) 37%, (2) 68% (patients with no PONV, graph data only) (i): (1) 67%, (2) 52% (patients with no PONV, graph data only)	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Eriksson and Korttila, 1996,[69] Finland RCT	(1) Propofol, desflurane, N_2O (n = 30) (2) Propofol, desflurane, N_2O, ondansetron (n = 30) (3) Propofol TIVA + N_2O (n = 30) N_2O: given Premedication: none Procedures: gynaecological laparoscopy Age: 18–45 years	(a) Open eyes (b) Orientation (c) Obey command (d) Sit unaided (e) Discharge/ street-fit (f) PONV (g) Maddox Wing (h) DSST	(a): (1) 3.9, (2) 4.3, (3) 5.1 min (b): (1) 5.0, (2) 6.5, (3) 6.4 min (c): (1) 4.8, (2) 5.2, (3) 5.7 min (d): (1) 36, (2) 28, (3) 27 min (e): (1) 372, (2) 109, (3) 110 min; $p < 0.01$ (group 1 faster) (f): (1) 80%, (2) 40%, (3) 20%; $p < 0.01$ (g): No difference (h): No difference	Grade I Method of randomisation not reported Double-blind
Fabbri *et al.*, 1995,[70] Italy RCT	(1) Propofol TIVA, N_2O, fentanyl (n = 30) (2) Propofol TIVA, N_2O, ketamine (n = 30) N_2O: given Premedication: none Procedures: urological endoscopy Gender: mix not stated Age: 60–75 years	(a) Alertness (b) Obey commands	(a): (1) 5.3, (2) 4.9; $p < 0.05$ (b): (1) 4.9, (2) 3.5 min; NS	Grade I Method of randomisation not reported Not blind
Felts *et al.*, 1990,[71] USA RCT	(1) N_2O 4 l/min, O_2 2 l/min, enflurane titrated to 4% or less (n = 89) (2) Air 4 l/min, O_2 1.5 l/min, enflurane titrated to 4% or less (n = 96) Procedures: laparoscopic tubal ligation Gender: women Age: 20–45 years	(a) PONV	(a): (1) 29.2%, (2) 9.4%; $p < 0.001$	Grade II–1a Randomisation divided by registration number
Fish *et al.*, 1999,[72] England RCT	(1) Sevoflurane/sevoflurane + alfentanil (n = 35) (2) Propofol TIVA + remifentanil (n = 36) N_2O: not given Premedication: none Procedures: urological surgery Gender: 85% men Mean ± SD age: 63.8 ± 14.3 years	(a) Open eyes (b) Verbal response (c) Aldrete score of 9 (d) PONV	(a): (1) 8, (2) 6 min (b): (1) 8, (2) 7 min (c): (1) 10, (2) 8 min (d): (1) 1%, (2) 1% No results significant	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Fletcher *et al.*, 1991,[73] USA RCT	(1) Thiopentone, desflurane, N_2O (n = 20) (2) Thiopentone, isoflurane, N_2O (n = 20) (3) Thiopentone, desflurane, no N_2O (n = 20) (4) Desflurane, desflurane, no N_2O (n = 20) N_2O: given in groups 1 and 2 Premedication: none Procedures: mixed Gender: not reported Mean ± SD age: 40.7 ± 1.3 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sedation (subjective 4-point scale) (e) Choice routine time (f) CFFT (g) PONV	(a, b, c): Only graph data given. Group 4 fastest; $p < 0.05$. Group 1 faster than groups 2 and 3; $p < 0.05$. Group 2 slowest (d): Group 2 best at 30 min. Groups 2 and 3 best at 60 min. No other differences (e, f, g): No differences	Grade I Method of randomisation not reported Blind
Fredman *et al.*, 1995,[74] USA RCT	(1) Propofol TIVA (n = 50) (2) Propofol, sevoflurane (n = 48) (3) Sevoflurane, sevoflurane (n = 48) N_2O: given Premedication: none Fentanyl Vecuronium Procedures: gynaecology, ENT Gender: 78% women Mean ± SD age: 36 ± 12 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sit unaided (e) Walk (f) Discharge (g) PONV (h) DSST	(a): (1) 9, (2) 9, (3) 10 min; NS (b): (1) 11, (2) 12, (3) 12 min; NS (c): (1) 13, (2) 13, (3) 15 min; NS (d): (1) 108, (2) 107, (3) 116 min; NS (e): (1) 146, (2) 156, (3) 165 min; NS (f): (1) 183, (2) 184, (3) 207 min; NS (g1): (1) 27%, (2) 30%, (3) 56%; NS (g2): (1) 10%, (2) 18%, (3) 33%; $p < 0.05$ (h): No differences	Grade I Method of randomisation not reported Blind
Green Gand Jonsson, 1993,[75] Sweden Controlled study	(1) Propofol, isoflurane + N_2O (n = 32) (2) Propofol TIVA for 25 min, then isoflurane + N_2O (n = 31) (3) Propofol TIVA + N_2O (n = 32) N_2O: given Premedication: none Procedures: arthroscopy, laparoscopy Gender: 79% women Mean ± SD age: 36 ± 8.7 years	(a) Open eyes (b) Orientation (c) Maddox Wing (d) Choice reaction time (e) P-deletion test (f) PONV	(a): (1) 9.7, (2) 11.3, (3) 11.0 min; $p < 0.05$ (b): (1) 11.0, (2) 13.4, (3) 13.1 min; $p < 0.05$ (c): No differences (d): No differences (e): No differences (f): Group 1 significantly more (data not given)	Grade II–1a Not clear whether randomisation was carried out

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Gunawardene and White, 1988,[76] England RCT	(1) Propofol TIVA, no N_2O (n = 30) (2) Propofol TIVA + N_2O (n = 30) (3) Propofol induction, enflurane + N_2O (n = 30) N_2O: given in groups 2 and 3 Premedication: 12 patients received temazepam Procedures: gynaecology Age: 22–67 years	(a) PONV only	No significant difference	Grade I Method of randomisation not reported Blind
Gupta *et al.*, 1992,[77] Sweden RCT	(1) Thiopentone, isoflurane (n = 16) (2) Propofol, isoflurane (n = 14) N_2O: not given Premedication: none Procedures: arthroscopy Gender: 23% women Age: 17–49 years	(a) Simple reaction time (b) Choice reaction time (c) Perception accuracy test (d) DSST (e) Clinical recovery (subjective, scale 1–5) (f) PONV	Raw data not supplied, only graphs (a–e): Thiopentone significantly more than propofol at 30 min; $p < 0.05$ No other differences	Grade I Method of randomisation not reported Not blind
Gupta *et al.*, 1995,[78] Sweden RCT	(1) Propofol TIVA (n = 25) (2) Propofol, isoflurane (n = 25) N_2O: given Premedication: none Analgesia: alfentanil Procedures: knee arthroscopy Gender: 44% women Age: 15–45 years	(a) P-deletion test (b) Trieger Dot Test (c) Steward score (d) Time to open eyes (e) PONV (f) Time to discharge	(a): (1) 24, (2) 33; $p < 0.05$ (controls 32) (b): (1) 11.6, (2) 7.5; $p < 0.01$ (controls (1) 3.5, (2) 3.3) (c): No difference (d): No difference (e): (1) 4%, (2) 15% (f): No difference	Grade I Method of randomisation not reported Blind assessment of recovery Also examined Mood Adjective Checklist preoperatively and at 2 and 24 h postoperatively
Gupta *et al.*, 1996,[79] Sweden RCT	(1) Propofol, desflurane, N_2O (n = 25) (2) Propofol, isoflurane, N_2O (n = 25) N_2O: given Premedication: none Alfentanil Procedures: arthroscopy Gender; 30% women Mean ± SD age: 30.6 ± 8.9 years	(a) Open eyes (b) Orientation (c) Finger tapping (d) Perceptive accuracy (e) PONV	(a): (1) 255, (2) 327 s; $p < 0.05$ (b): (1) 301, (2) 362 s; $p < 0.05$ (c): No difference (d): No difference (graph data only) (e): (1) 5%, (2) 3%; NS	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Haley *et al.*, 1988,[80] Canada RCT	(1) Thiopentone, alfentanil, N_2O (n = 20) (2) Thiopentone, fentanyl, N_2O (n = 20) (3) Thiopentone, enflurane, N_2O (n = 19) N_2O: given Premedication: none Procedures: minor gynaecological surgery Age: 18–60 years	(a) Respond to command (b) Orientation	(a): (1) 2.8, (2) 4.7, (3) 8.1 min (b): (1) 5.6, (2) 7.7, (3) 10.8 min No difference between groups	Grade I Method of randomisation not reported Not blind PONV not measured
Hough and Sweeney, 1998,[81] England RCT	(1) Propofol, isoflurane, N_2O (n = 80) (2) Propofol, desflurane, N_2O (n = 76) N_2O: given Premedication: none Fentanyl: to all patients Procedures: knee arthroscopy Gender: 33% women Age: 16–70 years	PONV only measured	No vomiting Nausea only Desflurane 14/76 Isoflurane 4/80 $p < 0.05$	Grade I Method of randomisation not reported Not blind
Hovorka *et al.*, 1989,[82] Finland RCT	(1) Isoflurane, N_2O, O_2 (n = 50) (2) Enflurane, N_2O, O_2 (n = 50) (3) Isoflurane, air, O_2 (n = 50) Premedication: oxycodone Procedures: gynaecological laparoscopy Gender: women Mean age: 33 years	(a) PONV	(a): (1) 54%, (2) 48%, (3) 52%; NS	Grade II–1a Pseudo-randomisation by date of birth Single blind
Huma, 1990,[83] Kenya RCT	(1) Propofol, halothane, N_2O (n = 20) (2) Thiopentone, halothane, N_2O (n = 20) N_2O: given Premedication: none Procedures: not reported Age: 16–65 years	(a) Eye opening (b) PONV	No difference between groups	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Jakobsson *et al.*, 1997,[84] Sweden RCT	Fentanyl: 1–2 µg/kg (1) Propofol induction/TIVA (n = 20) (2) Propofol induction, desflurane maintenance (n = 20) N_2O/O_2: given in 66% Premedication: 5 mg midazolam Procedures: arthroscopy Gender: 50% women Mean ± SD age: 34 ± 13 years	(a) Time in recovery room (b) Time to discharge (c) PONV (d) Pain	(a): NS (b): NS (c): NS (d): NS	Grade I Method of randomisation not reported Not blind
Kashtan *et al.*, 1990,[85] Canada RCT	(1) Propofol TIVA (n = 30) (2) Thiopentone TIVA (n = 30) N_2O: not given Premedication: none Procedures: not reported Gender: 85% women Mean ± SD age: 36.7 ± 9 years	(a) Open eyes (b) Obey command (c) Orientation (d) Walk (e) P-deletion test (f) Trieger Dot Test (g) PONV	(a): (1) 6.4, (2) 13.9 min; $p < 0.02$ (b): (1) 7.6, (2) 15.4 min; $p < 0.03$ (c): (1) 22.7, (2) 36.2 min; $p < 0.01$ (d): (1) 45, (2) 41; NS (e): No differences (f): Bilateral: (1) 2.5, (2) 2.7; postoperatively, (1) 6.0, (2) 10.3; $p < 0.05$ (g): No differences	Grade I Method of randomisation not reported Blind
Killian *et al.*, 1992,[86] Canada RCT	(1) Propofol TIVA (n = 33: 25 women, 8 men) (2) Thiopentone/isoflurane (n = 30: 24 women, 6 men) N_2O: given Premedication: none Procedures: gynaecology, orthopaedic, other day surgery Age: 18–65 years	(a) Time to eye open (b) Aldrete score (c) Time to orientation (d) Time to bathroom (e) Time to fluids (f) Time to discharge (g) P-deletion test (h) Nausea (i) Vomiting (j) Overall recovery	(a): (1) 8.4, (2) 8.7 min; NS (b): (1) 13, (2) 13; NS (c): (1) 14.9, (2) 15.4 min; NS (d): (1) 112, (2) 142 min; $p < 0.01$ (e): (1) 71, (2) 101 min; $p < 0.01$ (f): (1) 34, (2) 163 min; $p < 0.02$ (g): (1) –2, (2) –3; NS (h): (1) 1.36%, (2) 1.52%; NS (i): (1) 1.36%, (2) 1.52%; NS (j): (1) 4.55, (2) 3.97; $p < 0.01$	Grade I Randomisation by tables Not blind 12/75 patients excluded: prior to statistical analysis

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Korttila *et al.*, 1992,[87] USA RCT	(1) Propofol induction, propofol repeat 3 min later (n = 6) (2) Thiopentone induction, thiopentone repeat 3 min later (n = 6) N_2O: not given Premedication: none Gender: men volunteers	(a) Respond to command (b) Body sway (c) Choice reaction time (d) Co-ordination/ computer (e) DSST (f) Maddox Wing (g) Computer steering wheel (h) CFFT	(a): (1) 13.9, (2) 18.0 min; $p < 0.05$ (b–h): Data given as graphs only. Thiopentone more than propofol at 1 and 3 h; $p < 0.05$. Returned to control by 7 h	Grade I Method of randomisation not reported Double-blind Crossover Volunteers
Korttila *et al.*, 1990,[88] USA RCT	(1) Propofol TIVA (n = 21) (2) Thiopentone, isoflurane (n = 20) N_2O: given Premedication: none Procedures: gynaecology, general Gender: 83% women	(a) Obey command (b) Orientation (c) Sit unaided (d) Discharge (e) Perceptive accuracy (f) Finger tapping (g) Maddox Wing (h) PONV	(a): (1) 3.7, (2) 6.2 min; $p < 0.05$ (b): (1) 5.7, (2) 10.0 min; $p < 0.05$ (c): (1) 58, (2) 77 min; NS (d): (1) 136, (2) 204 min; $p < 0.05$ (e): (1) 102, (2) 136 min; $p < 0.05$ (f): (1) 104, (2) 124; NS (g): (1) 112, (2) 140; NS (h): (1) 7/20 15/20; $p < 0.05$	Grade I Method of randomisation not reported Blind
Larsen *et al.*, 1992,[99] Sweden RCT	(1) Propofol TIVA (n = 15: 12 men) (2) Propofol/isoflurane (n = 15: 9 men) N_2O: not given Premedication: none Procedures: knee arthroscopy Age: 18–45 years	(a) Choice reaction time (b) Perceptive accuracy test	(a): No differences (b): $p < 0.05$	Grade I Method of randomisation not reported

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Lebenbom-Mansour *et al.*, 1993,[90] USA RCT	(1) Propofol, desflurane, N_2O (n = 16) (2) Propofol TIVA, N_2O (n = 14) (3) Desflurane, desflurane, N_2O (n = 16) (4) Desflurane, desflurane, no N_2O (n = 14) N_2O: given in groups 1–3 Premedication: none Procedures: peripheral orthopaedic surgery Gender: 22% women Age: 18–65 years	(a) Open eyes (b) Obey command (c) Orientation (d) Walk (e) Discharge (f) P-deletion test (g) DSST (h) PONV	(a): (1) 7.7, (2) 10, (3) 7.8, (4) 4.2 min; $p < 0.05$. Group 4 significantly faster than others (b): (1) 9.1, (2) 12.2, (3) 8.0, (4) 4.4 min; $p < 0.05$. Group 4 significantly faster than others (c): (1) 10.2, (2) 8.9, (3) 9.6, (4) 5.6 min; $p < 0.05$. Group 4 significantly faster than others (d): (1) 127, (2) 93.6, (3) 132, (4) 93.6 min; $p < 0.05$. Group 4 significantly faster than others (e): (1) 163, (2) 110, (3) 159, (4) 120 min (f): No differences (g): No differences (h): Actual data not given. Groups 3 and 4 worse than group 1, which was worse than group 2	Grade I Method of randomisation not reported Blind
Lim and Low, 1992,[91] Singapore RCT	(1) Thiopentone, isoflurane (n = 25) (2) Propofol TIVA, N_2O (n = 25) N_2O: given in group 2 Premedication: none Procedures: dental day surgery Gender: 60% women Mean ± SD age: 17.8 ± 4.7 years	(a) Awakening (b) Orientation (c) Sitting unaided (d) Walking	(a): (1) 4.1, (2) 2.6 min; $p < 0.01$ (b): (1) 24.4, (2) 15.2 min; $p < 0.01$ (c): (1) 42, (2) 25 min; $p < 0.01$ (d): (1) 141, (2) 209 min; $p < 0.01$	Grade I Method of randomisation not reported Blind
Lindekaer *et al.*, 1995,[92] Denmark RCT	(1) Propofol, alfentanil, vecuronium, N_2O (n = 21) (2) Propofol, alfentanil, vecuronium, no N_2O (n = 21) Premedication: none Procedures: inguinal herniotomy Gender: 90% men Age: 18–60 years	(a) Open eyes (b) Orientation (c) PONV (d) Con-centration (e) Coordination (post-box) (f) Coordination (keyboard) (g) Short-term memory	(a): (1) 13.1, (2) 8.1 min; $p < 0.01$ (b): (1) 16.2, (2) 11.6 min; $p < 0.05$ (c): No differences (d–g): No differences	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Marshall *et al.*, 1992,[93] England RCT	(1) Propofol, isoflurane (n = 32) (2) Propofol TIVA + alfentanil + N_2O (n = 32) (3) Propofol, isoflurane (n = 25) (4) Propofol TIVA + N_2O, no alfentanil (n = 26) N_2O: given in groups 2 and 4 Premedication: none Procedures: gynaecological laparoscopy	(a) Awakening (b) Orientation (c) Picture memory (d) Simple reaction time (e) Computer dot tracker (f) PONV	(a): (1) 6.9, (2) 6.2, (3) 4.9, (4) 3.9 min; NS (b): (1) 8.0, (2) 7.3, (3) 6.1, (4) 5.1 min; NS (c–f): No difference	Grade I Method of randomisation not reported Blind
Maitikainen *et al.*, 1998,[94] Finland RCT	(1) Spinal lidocaine (n = 55: 30 women, 25 men) (2) Propofol TIVA (n = 32: 20 women, 12 men) (3) Propofol/isoflurane (n = 38: 14 women, 24 men) (4) Propofol/desflurane (n = 48: 18 women, 30 men) N_2O: not given Premedication: alfentanil Procedures: knee arthroscopy Age: 18–65 years	(a) Time to eye opening (b) Time to orientation (c) Pain (d) Alertness (e) Nausea (f) Time to discharge	(a): (1) NA, (2) 11, (3) 12, (4) 8 min; NS (b): (1) NA, (2) 13, (3) 13, (4) 9 min; NS (c): Figures but no data values reported (less pain $p < 0.001$ for group 1) (d): Figures but no data values reported (more sedated $p < 0.001$ for groups 1 and 4) (e): NS (no data reported) (f): (1) 168, (2) 55, (3) 56, (4) 46: $p < 0.001$ for group 1	Grade I Method of randomisation not reported Not blind
Martikainen *et al.*, 2000,[95] Finland RCT	(1) Spinal (n = 55) (2) Propofol/propofol TIVA (n = 32) (3) Propofol/isoflurane (n = 38) (4) Propofol/desflurane (n = 48) N_2O: not given Premedication: none Procedures: arthroscopic knee surgery Gender: 50% women Age: 16–65 years	(a) PONV (b) Pain (c) Satisfaction (subjective)	No significant difference	Grade I Method of randomisation not reported Not blind
Martikainen *et al.*, 2000,[95] Finland RCT	Same patient group as Martikainen *et al.* (2000a)	Street fit	No difference between groups 2, 3 and 4 Group 1 longer; $p < 0.01$	Grade I Method of randomisation not reported Not blind Not much detail Poorly reported study

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Melnick and Johnson, 1987,[96] USA RCT	(1) Isoflurane, no N_2O (n = 30) (2) Isoflurane + N_2O (n = 30) N_2O: given in group 2 Premedication: none Procedures: minor gynaecology	(a) Drowsiness (b) PONV	(a): NS (b): (1) 1%, (2) 8%; $p < 0.05$	Grade I Method of randomisation not reported Blind
Moffat and Cullen, 1995,[97] Scotland RCT	(1) Propofol TIVA, TCI, spontaneous ventilation (n = 20) (2) Etomidate, isoflurane, IPPV (n = 20) N_2O: given Premedication: none Opioid: fentanyl on induction Procedures: cataracts Gender: not reported Age: > 60 years	(a) Mini Mental State Examination (MMSE) (b) Time to spontaneous eye opening (c) Time to give correct date of birth	(a): No change (b): (1) 15, (2) 8 min (c): (1) 17, (2) 11 min; $p < 0.01$	Grade II–1a Method of randomisation not reported Questionable comparability of techniques
Naidu-Sjosvaad *et al.*, 1998,[98] Sweden RCT	(1) Propofol, desflurane (n = 25) (2) Propofol, sevoflurane (n = 25) N_2O: not given Premedication: none Procedures: videoarthroscopy (knee) Gender: 22% women Age:18–45 years	(a) Open eyes (b) Orientation (c) Sit unaided (d) DSST (e) Simple reaction time (f) Perceptive accuracy	(a): (1) 504, (2) 744 s; $p < 0.001$ (b): (1) 526, (2) 818 s; $p < 0.001$ (c): (1) 24, (2) 76 min; NS (d): No difference (graph data only) (e): No difference (graph data only) (f): Group 2 more at 15 and 45 min; $p < 0.01$ (graph data only)	Grade I Method of randomisation not reported Blind
Nathan *et al.*, 1998,[99] France RCT	(1) Alfentanil, sevoflurane, sevoflurane, N_2O (n = 26) (2) Alfentanil, propofol, propofol, N_2O (n = 26) N_2O: given Premedication: lorazepam Procedures: elective termination of pregnancy	(a) Subjective views of patients (b) PONV	(a): Cannot be summarised (b) NS	Grade I Method of randomisation: 'sealed envelopes' Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Nathanson *et al.*, 1995,[100] USA Controlled study	(1) Propofol, sevoflurane, N_2O (n = 21) (2) Propofol, desflurane, N_2O (n = 21) N_2O: given Premedication: none Opioid: vecuronium, fentanyl Procedures: laparoscopic sterilisation	(a) Open eyes (b) Obey command (c) Orientation (d) Sit unaided (e) Walk (f) Discharge	(a): (1) 7.8, (2) 4.8 min; $p < 0.05$ (b): (1) 10.2, (2) 6.4 min; NS (c): (1) 11.2, (2) 9.3 min; NS (d): (1) 90, (2) 107 min; NS (e): (1) 124, (2) 126 min; NS (f): (1) 193, (2) 201 min; NS	Grade II–1b
Nelskyla *et al.*, 1999,[101] Finland RCT	(1) Sevoflurane (n = 22) (2) Propofol + alfentanil (n = 22) N_2O: given Premedication: none Procedures; evacuation Age: > 18 years; mean ± SD, 28 ± 30 years	(a) PONV (b) Pain (c) Time to eyes open (d) Time to orientation (e) Time to fluids (f) Time to discharge (g) Patient satisfaction	(a): (1) 6%, (2) 1%; $p < 0.01$ (b): (1) 21, (2) 19; NS (c): (1) 6.5, (2) 3.5 min; $p < 0.05$ (d): (1) 7.5, (2) 5.0 min; $p < 0.05$ (e): (1) 30, (2) 22 min; NS (f): (1) 149, (2) 166 min; NS (g): (1) 86%, (2) 100%; NS	Grade I Randomisation by sequential coded envelopes Not blind
Nielsen *et al.*, 1991,[102] Denmark RCT	(1) Propofol TIVA, alfentanil (n = 28) (2) Thiopentone TIVA, alfentanil (n = 28) N_2O: not given Premedication: none Gender: women Age: 18–60 years	(a) P-deletion variant (b) Coordination post-box (c) Coordination pegboard (d) Short-term memory (e) Long-term memory	Data only given for all tests 2 h postoperatively (a–d): No differences (e): No recollection of picture used; (1) 5, (2) 13; $p < 0.05$	Grade I Method of randomisation not reported Blind
Nightingale and Lewis, 1992,[103] England RCT	(1) Propofol TIVA, alfentanil, no N_2O (n = 25) (2) Propofol, isoflurane, N_2O, alfentanil (n = 25) N_2O: given in group 1 Premedication: none Procedures: minor gynaecological Gender: women	(a) Simple reaction time (b) Choice reaction time (c) CFFT (d) PONV	No significant difference between groups for any variable	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
O'Hara *et al.*, 1996,[104] USA RCT	(1) Thiopentone, sevoflurane, N_2O (n = 25) (2) Thiopentone, isoflurane, N_2O (n = 22) N_2O: given Premedication: none Procedures: "generally gynaecology" Gender: women Mean ± SD age: 34.3 ± 1.2 years	(a) Open eyes (b) Orientation (c) Discharge (d) PONV (%) (e) DSST	(a): (1) 9.7, (2) 11.9 min; NS (b): (1) 13.6, (2) 17 min; p = 0.02 (c): (1) 244, (2) 282 min; NS (d): (1) 64%, (2) 54%; NS (e): No differences (graph data only)	Grade I Method of randomisation not reported Not blind
Oikkonen, 1994,[105] Finland RCT	(1) Alfentanil, propofol, suxamethonium, alfentanil, propofol TIVA (n = 15) (2) Alfentanil, propofol, suxamethonium, alfentanil, isoflurane (n = 15) N_2O: not given Premedication: diazepam, glyco., alcuronium Procedures: gynaecological laparoscopy Mean ± SD age: 38 ± 6 years	(a) Open eyes/ waken (b) Name, date of birth (c) Obey command (d) P-deletion test	(a–c): Data given on the number of patients fulfilling the criteria at a number of specified times. Group 1 better than group 2; $p < 0.01$ in all cases (d): NS	Grade I Method of randomisation not reported Not blind
Ong *et al.*, 2000,[106] Singapore RCT	(1) Fentanyl, propofol, propofol TIVA, no N_2O (n = 40) (2) Sevoflurane + N_2O (n = 40) N_2O: given in group 2 Premedication: none Procedures: minor gynaecological	(a) Open eyes (b) Orientation (c) PONV	(a): (1) 307, (2) 440 s; NS (b): (1) 346, (2) 427 s; NS (c): (1) 0%, (2) 2.5%; NS	Grade I Method of randomisation not reported Not blind
Patil *et al.*, 1999,[107] Mumbai RCT	(1) Sevoflurane (n = 39: 4 women, 35 men) (2) Thiopentone (n = 39: 7 women, 32 men) N_2O: given in group A Premedication: none Procedures: laryngoscopy Age: > 18 years; mean ± SD 56 ± 57 years	(a) Time to induction (b) PONV (c) Recovery (d) Tandem walking test (able to walk at 30 min)	(a): (1) 42.7, (2) 44.2 min; NS (b): (1) 0%, (2) 1%; NS (c): (1) 9.7, (2) 11.2 min; p = 0028 (d): (1) 22, (2) 12; $p < 0.05$ Incidence of arrhythmias higher in group 2; $p < 0.05$	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Philip *et al.*, 1996,[108] USA RCT	(1) Propofol, sevoflurane, N_2O (n = 149) (2) Propofol, isoflurane, N_2O (n = 97) N_2O: given Premedication: none Procedures: mixed Gender: 80% women Mean ± SD age: 33 ± 10 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sit unaided (e) Walk (f) Discharge (g) DSST (h) PONV	(a): (1) 7, (2) 9 min; $p < 0.05$ (b): (1) 8, (2) 10 min; $p < 0.05$ (c): (1) 9, (2) 12 min; $p < 0.05$ (d): (1) 51, (2) 62 min (e): (1) 64, (2) 69 min (f): (1) 162, (2) 184 min (g): Preoperative (1) 56%, (2) 37%; $p < 0.05$. Post-operative (1) 86%, (2) 75% (h): (1) 36%, (2) 51%; $p < 0.05$	Grade I Method of randomisation not reported Not blind
Pollard *et al.*, 1994,[109] UK RCT	(1) Propofol, halothane, N_2O (n = 26) (2) Propofol, enflurane, N_2O (n = 27) (3) Propofol, isoflurane, N_2O (n = 26) (4) Propofol TIVA, N_2O (n = 26) N_2O: given Premedication: none Procedures: oral surgery Gender: 18% women Age: 19–45 years	(a) Mood/ stress/anxiety (b) Choice reaction time (c) Maddox Wing (d) Discharge time	Groups 1 and 2 showed better recovery than groups 3 and 4	Grade I Method of randomisation not reported Not blind
Power, 1989,[110] England RCT	(1) Propofol, isoflurane, N_2O, spontaneous ventilation (n = 30) (2) Propofol, isoflurane, N_2O (n = 30) N_2O: given Premedication: none IPPV: atracurium Procedures: oral surgery Gender: 70% women Mean ± SD age: 22.8 ± 1 years	(a) Post-box (b) P-deletion test (c) Eye opening (d) Orientation (e) PONV (%)	(a): (1) 35.2, (2) 33.8; NS (b): No differences between groups (c): (1) 10.1, (2) 4.0 min; $p < 0.001$ (d): (1) 12.6, (2) 7.0 min; $p < 0.001$ (e): (1) 17%, (2) 13%; NS	Grade I Method of randomisation not reported Blind
Price *et al.*, 1988,[111] England RCT	(1) Fentanyl, propofol TIVA, no N_2O (n = 49) (2) Fentanyl, thiopentone, N_2O, enflurane (n = 49) N_2O: given in group 2 Premedication: none Procedures: D&C, elective termination of pregnancy	(a) Early recovery (b) Orientation (c) Steward score (d) PONV	(a): (1) 4.6, (2) 5.1 min; NS (b): (1) 6.6, (2) 8.0 min; NS (c): (1) all maximum at 30 min ($p < 0.01$), (2) 5/50 not maximum at 30 min (d): (1) 2%, (2) 21%; $p < 0.001$	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Raeder *et al.*, 1997,[112] Denmark Ten-centre RCT	(1) Propofol, sevoflurane, N_2O (n = 84) (2) Propofol TIVA, N_2O (n = 85) N_2O: given Premedication: none Analgesia: fentanyl, diclofenac Procedures: knee arthroscopy Gender: 36% women Mean ± SD age: 32 ± 9.9 years	(a) Open eyes (b) Obey command (c) Orientation (d) Home ready (e) DSST (f) PONV	(a): (1) 6.1, (2) 7.2 min; $p < 0.05$ (b): (1) 6.9, (2) 8.2 min; $p < 0.05$ (c): (1) 7.7, (2) 9.0 min; $p < 0.05$ (d): (1) 155, (2) 143 min (e): Graph data only. Group 1 better than group 2 at 15 min; $p < 0.05$ (f): Group 1 worse than group 2; $p < 0.05$	Grade I Method of randomisation not reported Blind
Raeder *et al.*, 1998,[113] Denmark RCT	(1) Propofol, fentanyl–propofol TIVA (n = 30) (2) Propofol, fentanyl–desflurane (n = 30) N_2O: not given Premedication: midazolam, ondansetron, droperidol Analgesia: ketorolac, ketamine Procedures: laparoscopic cholecystectomy Gender: 80% women Age: not reported	(a) Open eyes (b) Date of birth (c) Sit unaided (d) PONV (e) Discharge	(a): (1) 9.6, (2) 6.4 min; $p < 0.04$ (b): (1) 9.6, (2) 8.4 min; $p < 0.02$ (c): (1) 71, (2) 73 min; NS (d): (1) 17, (2) 40 min; $p < 0.03$ (e): (1) 287%, (2) 278%; $p < 0.03$	Grade I Method of randomisation not reported Not blind
Raftery and Sherry, 1992,[114] England RCT	(1) Propofol TIVA (n = 41) (2) Propofol, enflurane, atracurium (n = 39) N_2O: given Premedication: none Analgesia: alfentanil 50 µg/kg IPPV Procedures: laparoscopy Gender: women	(a) Time to give date of birth (b) PONV	(a): No difference (b): (1) 1–3%, (2) 16–18% at 30 min; no difference at 2 and 6 h; (1) 4–16%, (2) 18–26%; overall $p < 0.05$	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Randel *et al.*, 1992,[115] USA RCT	(1) Thiamylal, enflurane (n = 30) (2) Propofol TIVA (n = 30) N_2O: given Premedication: none Anti-emetic: droperidol 0.6 mg, sufentanil 0.6 µg/kg Procedures: laparoscopy Gender: women Age: 18–45 years	(a) Eye opening (b) Orientated to day, date of birth (c) Time to ambulation (d) Time to voiding (e) Time to discharge (f) Nausea in recovery (g) Vomiting in recovery (h) Anti-emetics prescribed in recovery	(a): (1) 8.1, (2) 5.2 min; $p < 0.01$ (b): (1) 12.7, (2) 9.3 min; $p < 0.01$ (c): (1) 102.7, (2) 83.3 min; $p < 0.05$ (d): (1) 119.5, (2) 101.1 min; $p < 0.05$ (e): (1) 161.1, (2) 138.3 min; $p < 0.05$ (f): (1) 13, (2) 6; $p = 0.052$ (g): (1) 7, (2) 2; NS (h): (1) 4, (2) 1; NS	Grade I Method of randomisation not reported Blind
Rapp *et al.*, 1992,[116] USA RCT Multicentre	(1) Propofol, desflurane, N_2O (2) Propofol TIVA + N_2O (3) Desflurane, desflurane, N_2O (4) Desflurane, desflurane, no N_2O N_2O: given in groups 1–3 Premedication: none Procedures: peripheral orthopaedic surgery Gender: 30% women Mean ± SD age: 34 ± 10 years	(a) Open eyes (b) Obey command (c) Orientation (d) P-deletion test (e) DSST (f) PONV (g) Discharge	(a): (1) 10, (2) 9.7, (3) 7.3, (4) 9.7 min; NS (b): (1) 11, (2) 10.6, (3) 7.8, (4) 10.1 min; NS (c): (1) 12, (2) 11.3, (3) 9.6, (4) 10.7 min; NS (d, e): Data graphs only; no differences (f): (1) 41%, (2) 13%, (3) 67%, (4) 55%; $p < 0.002$ (g): (1) 143, (2) 130, (3) 148, (4) 161 min; NS	Grade I Method of randomisation not reported Blind
Reigle *et al.*, 1995,[117] USA RCT	(1) Propofol TIVA (n = 30) (2) Isoflurane (n = 30) N_2O: given in 70% Premedication: metoclopramide Procedures: gynaecological laparoscopy	(a) PONV	(a): Both groups NS. Some patients received pethidine and those had increased PONV	Grade I Method of randomisation not reported Blind
Ryom *et al.*, 1992,[118] Denmark RCT	(1) Thiopentone TIVA, fentanyl, N_2O (n = 40) (2) Propofol TIVA, fentanyl, N_2O (n = 40) N_2O: given Premedication: none Procedures: minor gynaecological surgery Age: 15–67 years	(a) Co-ordination, nose pointing test (b) Finger Tapping Test (c) Reaction time	No differences (only processed data given)	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Sampson *et al.*, 1988,[119] USA RCT	(1) Propofol TIVA (n = 19) (2) Thiamylal TIVA (n = 21) N_2O: given Premedication: none Procedures: elective termination of pregnancy Age:18–37 years	(a) Open eyes (b) Obey command (c) Orientation (d) PONV	(a): Graph data only (b): Group 2 worse than group 1; $p < 0.05$ (c): (1) 0%, (2) 5%; $p < 0.01$	Grade I Method of randomisation not reported Not blind
Sanders, 1991,[120] Wales RCT	(1) Propofol TIVA (n = 18) (2) Thiopentone TIVA, no N_2O (n = 8) N_2O: given in group (b) Premedication: none Procedures: minor gynaecological Age:16–65 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sit unaided (e) Stand unaided (f) Choice reaction time, DSST, dexterity (g) PONV	(a): (1) 6.7, (2) 21.4 min; $p < 0.001$ (b): (1) 7.3, (2) 22.1 min; $p < 0.001$ (c): (1) 8.7, (2) 23.2 min; $p < 0.001$ (d): (1) 43.0, (2) 77.8 min; $p < 0.05$ (e): (1) 80.0, (2) 115.2 min; $p < 0.05$ (f): NS at all time points (g): NS	Grade I Method of randomisation not reported Not blind
Santawat *et al.*, 1999,[227] Thailand RCT	(1) Fentanyl, propofol/propofol TIVA, no N_2O (n = 20) (2) Fentanyl, propofol/halothane, N_2O (n = 20) N_2O: given in group (b) Premedication: none Procedures: nasal fracture, dental surgery Age: 12–60 years	(a) Sit unaided (b) Orientation (c) Stand unaided (d) Number circling test (e) Accuracy of ball bearings into a tube (f) PONV	No significant difference with any test	Grade I Method of randomisation not reported Blind
Segatto *et al.*, 1993,[121] Italy RCT	(1) Propofol TIVA (n = 100) (2) Thiopentone/N_2O (65%) (n = 100) N_2O: given in group 2 Premedication: given Atropine 0.6 mg i.m. Supplementary: suxamethonium 1 mg/kg, fentanyl 2 µg/kg Procedures: uterine cerclage Gender: women, 20 weeks pregnant Mean ± SD age: 25.5 ± 9.1 years	(a) Eye opening (b) Answer questions (c) Steward score at 15 min (d) PONV (e) Euphoria (f) Depression (g) Personal preference of patient (h) Neonatal abnormalities	(a): 5.1 min; $p < 0.01$ (b): 7.5 min; $p < 0.01$ (c): (1) 100%, (2) 65%; $p < 0.01$ (d): (1) 21%, (2) 35%; NS (e): (1) 16, (2) 4; $p < 0.01$ (f): (1) 8, (2) 22; $p < 0.05$ (g): NS (h): (1) 9, (2) 16; NS	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Short *et al.*, 1985,[122] UK RCT	(1) Methohexitone, alfentanil, N_2O, O_2 (n = 20: 14 women, 6 men) (2) Methohexitone, isoflurane, O_2 (n = 20: 8 women, 3 men) (3) Methohexitone, isoflurane, N_2O, O_2 (n = 20: 10 women, 10 men) N_2O: given in groups 1 and 3 Premedication: none Procedures: D&C, cystourethroscopy Age: > 18 years; mean (1) 45, (2) 46, (3) 43 years	(a) Time to open eyes (b) Time to recall date of birth (c) Time to recall name (d) Post-box test (e) P-deletion test	Group 2 abandoned after 11 patients due to poor conditions during induction (a): (1) 9.2, (3) 9.1 min; $p < 0.01$ (b): (1) 9.9, (3) 9.7 min; $p < 0.01$ (c): (1) 9.5, (3) 9.6 min; $p < 0.01$ (d): (1) 34.3, (2) 44.3, (3) 40.3; $p < 0.01$ group 2 (e): (1) 4; (2) 2; (3) 2; NS	Grade I Method of randomisation not reported Not blind The majority of group 2 patients were not able to complete the trial
Sivalingam *et al.*, 1999,[123] Singapore RCT	ASA grade I or II (1) Propofol 2.5 mg/kg + 10 mg increments i.v. (n = 25) (2) Sevoflurane 8% + 60% N_2O vital capacity breath (n = 25) (3) Sevoflurane as (2) + alfentanil 5 µg/kg (n = 25) (4) Propofol as (1) + alfentanil 5 µg/kg (n = 25) N_2O: given in groups 2 and 3 Premedication: none Procedures: mixed Gender: 55% men Age: 16–65 years	LMA insertion (quality for induction only): excellent, satisfactory or poor	Satisfactory or excellent: (1) 64%, (2) 64%, (3) 100%, (4) 88%; $p < 0.001$	Grade I Method of randomisation not reported Open
Sloan *et al.*, 1996,[124] USA RCT	(1) Sevoflurane/sevoflurane + N_2O (n = 25) (2) Isoflurane/isoflurane + N_2O (n = 25) N_2O: given Premedication: none Procedures: not reported Age: 18–76 years	(a) Open eyes (b) Obey command (c) Orientation (d) Discharge (e) DSST	(a): (1) 8.1, (2) 10.6 min (b): (1) 8.0, (2) 9.9 min (c): (1) 9.9, (2) 12.6 min (d): (1) 120, (2) 133 min (e): Data not given No difference between groups	Grade I Method of randomisation not reported Not blind
Smith and Thwaites, 1999,[125] England RCT	(1) Sevoflurane./sevoflurane (n = 30) (2) Propofol TCI (n = 31) N_2O: not given Premedication: none Procedures: mixed Gender: 66% women Age: 18–73 years	(a) Open eyes (b) Date of birth (c) Sit up (d) Walk (e) Street fit (f) PONV	(a): 7.1 min; $p = 0.027$ (b): 8.1 min; NS (c): 100 min; $p = 0.024$ (d): 175 min; NS (e): 193 min; $p = 0.005$ (f): (1) 9%; (2) 1%; $p = 0.006$	Grade I Method of randomisation: computer-generated random numbers Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Song *et al.*, 1998,[126] USA RCT	(1) Propofol, desflurane + N_2O (n = 40) (2) Propofol, sevoflurane + N_2O (n = 40) (3) Propofol TIVA + N_2O (n = 40) N_2O: given Premedication: none Procedures; laparoscopic tubal ligation Mean ± SD age: 30 ± 5 years	(a) Awaken (b) Orientation (c) Home-ready (d) Discharge (e) PONV	(a): (1) 4.7, (2) 5.2, (3) 8.3 min; $p < 0.05$ (no difference between groups 1 and 2) (b): (1) 9.8, (2) 11.3, (3) 14.7 min; $p < 0.05$ (no difference between groups 1 and 2) (c): (1) 140, (2) 143, (3) 149 min (d): (1) 188, (2) 176, (3) 173 min (e): (1) 12%, (2) 8%, (3) 4% Groups 1 and 2 to group 3	Grade I Method of randomisation not reported Not blind
Sukhani *et al.*, 1994,[127] USA RCT	(1) Propofol TIVA, atracurium, IPPV, N_2O (n = 34) (2) Propofol TIVA, atracurium, IPPV, no N_2O (n = 36) N_2O: given in group 1 Premedication: none Procedures: gynaecologic laparoscopy Age: 19–40 years	(a) Open eyes (b) Orientation (c) Ambulation (d) Discharge (e) PONV	(a, b): Significantly shorter in group 2 (no data given); $p < 0.05$ (c, d): No difference (no data given) (e): No differences. Early (1) 1–8%, (2) 2–6%; over 24 h (1) 1–13%, (2) 2–6%	Grade I Method of randomisation not reported Not blind
Sukhani *et al.*, 1996,[128] USA RCT	(1) Propofol TIVA + N_2O + fentanyl (n = 40) (2) Propofol TIVA + N_2O + ketorolac (n = 40) N_2O: given Premedication: none Procedures: gynaecological laparoscopy Age: 19–40 years	(a) Open eyes (b) Orientation (c) Ambulation (d) Discharge (e) PONV Raw data not given	(a, b): No difference (c, d): Group 2 shorter; $p < 0.05$ (e): (1) 20%, (2) 11%; $p < 0.05$	Grade I Method of randomisation not reported Double-blind
Tang *et al.*, 1999,[129] USA RCT	(1) Propofol TIVA, no N_2O (n = 34) (2) Propofol TIVA, N_2O (n = 35) N_2O: given in group 2 Premedication: none Procedures: not reported Gender: not reported Mean ± SD age: 57 ± 18 years	(a) Open eyes (b) Orientation (c) Sit unaided (d) Stand unaided (e) Street-fit (f) PONV	(a): (1) 5, (2) 4 min (b): (1) 6, (2) 4 min (c): (1) 15, (2) 14 min (d): (1) 24, (2) 21 min (e): (1) 26, (2) 21 min (f): (1) 2%, (2) 1% No results significant	Grade I Method of randomisation: computer-generated random numbers Double-blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Tarazi and Philip, 1998,[130] USA RCT	Induction: fentanyl, ketorolac, propofol, vecuronium, suxamethonium (1) Induction: fentanyl, ketorolac, propofol, vecuronium, suxamethonium, sevoflurane + N_2O (n = 30) (2) Induction: fentanyl, ketorolac, propofol, vecuronium, suxamethonium, desflurane + N_2O (n = 30) N_2O: given Premedication: none Procedures: laparoscopic tubal ligation Mean ± SD age: 35 ± 4 years	(a) Open eyes (b) Obey command (c) Sit unaided (d) Walk unaided (e) Street-fit (f) DSST (g) PONV	(a): (1) 5, (2) 5 min (b): (1) 6, (2) 6 min (c): (1) 64, (2) 75 min (d): (1) 83, (2) 93 min (e): (1) 136, (2) 151 min (f): NS (g): NS No differences significant	Grade I Method of randomisation not reported Not blind
Tracey *et al.*, 1982,[131] England RCT	(1) Thiopentone, N_2O, halothane (n = 25) (2) Thiopentone, N_2O, enflurane (n = 25) (3) Thiopentone, N_2O, isoflurane (n = 25) N_2O: given Premedication: none Procedures: D&C, laparoscopy	(a) PONV	NS	Grade I Method of randomisation not reported Not blind
Valanne, 1992,[132] Finland RCT	(1) Propofol TIVA, N_2O (n = 25) (2) Propofol, isoflurane, N_2O (n = 25) N_2O: given Premedication: none Procedures: oral surgery Gender: 25% women Mean ± SD age: 29 ± 7.2 years	(a) Orientation (b) Straight line walking (No. of patients) (c) PONV (d) Perceptual speed test (variant of P-deletion test)	(a): (1) 11.0, (2) 16.5 min; $p < 0.01$ (b): (1) 25, (2) 14; $p < 0.01$ (c): (1) 25%, (2) 15%; $p < 0.001$ (d): No differences (no data given)	Grade I Method of randomisation not reported Not blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
van Hemelrijck *et al.*, 1991,[133] USA RCT	(1) Propofol TIVA + N_2O (n = 23) (2) Propofol, desflurane, N_2O (n = 23) (3) Desflurane, desflurane, N_2O (n = 23) (4) Desflurane, desflurane, no N_2O (n = 23) N_2O: give in groups 1–3 Premedication: none Procedures: gynaecologic laparoscopy Mean ± SD age: 31 ± 6 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sit unaided (e) Discharge (f) DSST (g) PONV	(a): (1) 7.3, (2) 5.1, (3) 5.9, (4) 4.5 min; $p < 0.05$ (group 1 against groups 2, 3 and 4) (b): (1) 8.3, (2) 6.4, (3) 7.0, (4) 5.1 min; $p < 0.05$ (group 1 against groups 2, 3 and 4) (c): (1) 10.2, (2) 8.3, (3) 9.0, (4) 6.7 min; $p < 0.05$ (group 1 against groups 2, 3 and 4) (d): (1) 89, (2) 101, (3) 94, (4) 89 min; NS (e): (1) 199, (2) 204, (3) 196, (4) 215 min; NS (f): No significant differences (data not given) (g): Group 1 significantly less than other three groups, which were equal (data not given)	Grade I Method of randomisation not reported Not blind
Wandel *et al.*, 1995,[134] Germany RCT	(1) Propofol TIVA + N_2O (n = 25) (2) Propofol, sevoflurane + N_2O (n = 25) N_2O: given Premedication: none Analgesia: fentanyl, vecuronium Procedures: not reported Gender: 60% men Mean ± SD age: 36.2 ± 14 years	(a) Open eyes (b) Obey command (c) Orientation (d) DSST	(a): (1) 9.8, (2) 6.6 min; $p < 0.01$ (b): (1) 12.6, (2) 7.2 min; $p < 0.01$ (c): (1) 14.6, (2) 8.6 min; $p < 0.01$ (d): Group 1 worse at 15 and 30 min only; $p < 0.01$ (graph data only)	Grade I Method of randomisation not reported Not blind
Werner and Newhouse, 1993,[135] USA RCT	(1) Methohexitone, isoflurane, N_2O (n = 25) (2) Propofol TIVA, N_2O (n = 25) N_2O: given Premedication: none Analgesia: alfentanil Procedures; dental day surgery Gender: not reported Age: not reported	(a) VAS of memory (subjective, by recovery staff) (b) Open eyes (c) Orientation (d) Sit unaided (e) Walk (f) PONV	(a): (1) 4.4, (2) 4.9; NS (b): (1) 7, (2) 6 min; NS (c): (1) 9, (2) 8 min; NS (d): (1) 14, (2) 13 min; NS (e): (1) 38, (2) 33 min; NS (f): (1) 16%, (2) 1%; $p < 0.05$	Grade I Method of randomisation not reported Blind

continued

***TABLE 66* contd** *Summary of adult clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Wetchler *et al.*, 1992,[136] USA RCT	**Study 1** (1) Propofol TIVA (n = 20) (2) Propofol, isoflurane (n = 20) (3) Thiopentone, isoflurane (n = 20) N_2O: given Premedication: none Analgesia: fentanyl Procedures; laparoscopy Age: not reported **Study 2** (1) Propofol TIVA (n = 50) (2) Thiopentone, isoflurane (n = 50) N_2O: given Analgesia: fentanyl Premedication: none Procedures: not reported Age: not reported	**Study 1** (a) PONV (Patton severity score) (b) Time to sitting independently (c) Tolerance of clear fluids (d) Trieger Dot Test (e) Aldrete score **Study 2** (a) Nausea (b) Vomiting	**Study 1** (a): (1) 18, (2) 68, (3) 96; $p < 0.001$ (b): (1) 32.9, (2) 39.8, (3) 49.1 min; $p < 0.01$ (c): Values not reported; $p < 0.01$ (d): No significant difference (e): No significant difference **Study 2** (a): (1) 10%, (2) 42%; $p < 0.002$ (b): (1) 3%, (2) 29%; $p < 0.02$	Grade I Method of randomisation not reported Not blind Very few details of the trial were reported
Wrigley *et al.*, 1991,[137] England RCT	(1) Propofol/desflurane N_2O (n = 15) (2) Propofol TIVA, N_2O (n = 15) (3) Desflurane, desflurane, N_2O (n = 15) (4) Desflurane, desflurane, no N_2O (n = 15) N_2O: given in groups 1–3 Premedication: none Procedures: orthopaedic surgery Age: 18–70 years	(a) Open eyes (b) Obey command (c) Orientation (d) Sit/stand (e) Discharge (f) P-deletion test (g) DSST (h) PONV	(a): (1) 8, (2) 8, (3) 9, (4) 6 min; NS (b): (1) 10, (2) 9, (3) 9, (4) 6 min; NS (c): (1) 13, (2) 12, (3) 11, (4) 8 min; NS (d): (1) 111, (2) 108, (3) 106, (4) 82 min; NS (e): No difference (f): Raw data not given (g): Group 2 worst, group 4 best (h): Desflurane group worse then propofol group (raw data not given)	Grade I Method of randomisation not reported Blind

CFFT, critical flicker fusion test; NNT, numbers needed to treat; PACU, postanaesthesia care unit; TCI, target controlled infusion

Appendix 5

Paediatric clinical outcomes studies

TABLE 67 *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Ariffin *et al.*, 1997,[138] UK RCT	(1) Sevoflurane (n = 40) (2) Halothane (n = 40) Induction and maintenance N_2O: given Procedures: dental extractions Age: 5–12 years	(a) Loss of eyelash reflex (b) Loss of jaw tone (c) Eye opening (d) Nausea after discharge	(a): (1) 89, (2) 127; $p < 0.05$ (b): (1) 125, (2) 146; $p < 0.05$ (c): (1) 167, (2) 102; $p < 0.05$ (d): (1) 3, (2) 10; $p < 0.05$ Discharge time/intraoperative and recovery complications: NS	Grade I No details of randomisation Gender and ASA data not given
Cheng *et al.*, 1998,[139] Taiwan RCT	(1) Propofol/ketamine (n = 32) (2) Thiopentone/halothane (n = 28) N_2O: not given Procedures: herniorrhaphy, hydrocelectomy Age: 2–7 years	Number of patients with: (a) pain on injection (b) apnoea (c) phlebitis (d) vomiting (e) involuntary movement	(a): (1) 12/32, (2) 2/28 (b): 1 (c): 2 (d): (1) 0, (2) 6; $p < 0.05$ (e): (1) 4, (2) 3	Grade II–1a No details on randomisation No differences were statistically significant, apart from vomiting
Crawford *et al.*, 1998,[140] Canada RCT	(1) Propofol (n = 18) (2) Propofol/N_2O (n = 17) (3) Halothane/N_2O (n = 19) Maintenance only Procedures: minor orthopaedic, urological, general surgical Age: 3–12 years	Time (min) to: (a) extubation (b) eye opening (c) obey command (d) fully awake (e) discharge (f) vomiting in unit (g) vomiting after discharge	(a): (1) 6.3, (2) 5.4, (3) 5.4; NS (b): (1) 11, (2) 11, (3) 18; $p < 0.05$ vs group 3 (c): (1) 13, (2) 12, (3) 21; $p < 0.05$ vs group 3 (d): (1) 21, (2) 21, (3) 35; $p < 0.05$ vs group 3 (e): (1) 50, (2) 45, (3) 9; NS (f): (1) 0, (2) 2, (3) 2; NS (g): (1) 3, (2) 7, (3) 10; $p < 0.05$ vs group 1	Grade I No details on randomisation

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Davis *et al.*, 1994,[142] USA RCT	(1) Desflurane (n = 22) (2) Halothane (n = 23) Maintenance only N_2O: given Procedures: inguinal hernia repair, orchidopexy, circumcision Mean ± SD age: 3 ± 2 years	Time (min) to: (a) discharge recovery (b) discharge home % Patients with: (c) delirium (d) PONV (e) airway problems	(a): (1) 21, (2) 29; NS (b): (1) 76, (2) 68; NS (c): (1) 50, (2) 21; p = 0.09 (d): (1) 13.6, (2) 13; NS (e): (1) 0, (2) 4.3; NS	Grade I Small numbers No differences were statistically significant
Davis *et al.*, 1997,[141] USA and Canada RCT multicentre	(1) Remifentanil (n = 62) (2) Alfentanil (n = 19) (3) Isoflurane (n = 22) (4) Propofol (n = 20) N_2O: given Procedures: strabismus surgery Age: 2–12 years	Time (min) to: (a) extubation (b) first movement (c) discharge home % Patients with: (d) vomiting (e) bradycardia (f) postoperative hypoxaemia	(a): (1) 10, (2) 10, (3) 10, (4) 11.5; NS (b): (1) 10, (2) 6, (3) 9, (4) 11.5; NS (c): (1) 139, (2) 140, (3) 141, (4) 123; NS (d): (1) 31, (2) 26, (3) 32, (4) 30; NS (e): (1) 12, (2) 0, (3) 5, (4) 0; NS (f): (1) 0, (2) 21, (3) 0, (4) 0; p < 0.05 Group 1 compared with group 2	Grade I PONV was not statistically significantly different for the four groups, but the PONV rate was high overall, due to the surgical procedure
Greenspun *et al.*, 1995,[143] USA RCT	(1) Sevoflurane (n = 21) (2) Halothane (n = 18) N_2O: given Procedures: ENT Age: 1–12 years	Time (min) to: (a) induction (b) emergence (c) recovery (d) discharge (e) PONV (%)	(a): (1) 1, (2) 1.4; p < 0.0002 (b): (1) 7.1, (2) 9.6; p < 0.04 (c): (1) 19.9, (2) 31.1; p < 0.0003 (d): (1) 143.7, (2) 134.7; NS (e): (1) 33, (2) 38; NS	Grade I Small numbers
Gurkan *et al.*, 1999,[144] Turkey RCT	(1) Propofol (n = 20) (2) Sevoflurane (n = 20) N_2O: given Procedures: strabismus surgery Age: 3–15 years	(a) Vomit (b) Total vomit (c) Anti-emetic Tx (d) Oculocardiac	(a): (1) 5, (2) 13; p < 0.05 (b): (1) 0.3, (2) 1.7; p < 0.01 (c): (1) 1, (2) 9; p < 0.05 (d): (1) 2, (2) 1; p < 0.05	Grade I Discharge times and admission rates not measured

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Hamunen *et al.*, 1997,[145] Finland RCT	(1) Thiopentone/isoflurane (*n* = 30) (2) Propofol 5 mg/kg (*n* = 29) (3) Propofol 10 mg/kg (*n* = 31) N_2O: given Procedures: strabismus surgery Age: 5–14 years	(a) Vomiting (%) (b) Time to first emesis (min)	(a): (1) 37, (2) 29, (3) 33; NS (b): (1) 427, (2) 393, (3) 434; NS	Grade I Patients stayed overnight after surgery
Hannallah *et al.*, 1994,[146] USA RCT	(1) Propofol/propofol (*n* = 25) (2) Propofol/halothane (*n* = 25) (3) Thiopentone/halothane (*n* = 25) (4) Halothane/halothane (*n* = 25) N_2O: given Procedures: eye, plastic, dental, urology Age: 3–12 years	Time (min) to: (a) extubation (b) recovery (c) discharge (d) PONV (hospital) (%) (e) PONV (home) (%)	(a): (1) 9, (2) 7, (3) 11, (4) 11; NS (b): (1) 22, (2) 29, (3) 36, (4) 31; NS (c): (1) 101, (2) 133, (3) 127, (4) 144; $p < 0.05$ (group 1 compared with groups 2, 3 and 4) (d): (1) 4, (2) 24, (3) 24, (4) 48; $p < 0.05$ (group 1 compared with groups 2, 3 and 4) (e): (1) 4, (2) 9, (3) 17, (4) 0; $p < 0.05$ (group 4 compared with groups 1, 2 and 3)	Grade I No details on randomisation
Johannesson *et al.*, 1995,[147] Sweden RCT	(1) Halothane (*n* = 18) (2) Sevoflurane (*n* = 22) N_2O: given Procedures: ENT Age: 1.1–7.5 years	Time (min) to: (a) intubation (b) response post-operatively (c) discharge (d) PONV (%)	(a): (1) 8.8, (2) 6.8; $p < 0.001$ (b): (1) 17, (2) 12; NS (c): (1) 89, (2) 86; NS (d): (1) 25, (2) 9; NS	Grade I Difference in excitement reported, patients receiving sevoflurane had higher levels of excitement
Kotiniemi and Ryhanen, 1996,[148] Finland RCT	Comparison of induction methods: (1) Intravenous (thiopentone) (*n* = 29) (2) Inhalational (halothane) (*n* = 28) (3) Rectal (methohexitone) (*n* = 29) N_2O: given with halothane maintenance Procedures: ENT Mean ± SD age: 4 ± 1.2 years	Time (min) from: (a) arrival to surgery (b) induction to surgery (c) emergence to recovery room discharge	(a): (1) 6.3, (2) 7.8, (3) 14.8; $p < 0.001$ (b): (1) 1.7, (2) 3.8, (3) 9.0; $p < 0.001$ (c): (1) 3.5, (2) 3.6, (3) 5.1; $p = 0.012$ PONV in hospital: 15% PONV postdischarge: 27% Mild pain at home on day of operation: 52% Pain lasting > 24 h: 18% Sleepy on day of operation: 69%; no differences between groups	Grade II–1a (See also appendix 7) No differences found

continued

TABLE 67 contd *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Lerman *et al.*, 1996,[149] Canada and USA Multicentre RCT	(1) Halothane (n = 125) (2) Sevoflurane (n = 250) N_2O: given Procedures: genitourinary, lower abdominal, plastic, orthopaedic Age: 1–12 years	Time (min) to: (a) induction (b) responds to commands (c) Aldrete score > 8 (d) tolerating oral fluids (e) suitable for discharge (f) PONV (%)	(a): (1) 1.3, (2) 1.6; $p < 0.001$ (b): (1) 12.3, (2) 19.9; $p < 0.001$ (c): (1) 19.3, (2) 24.8; $p < 0.001$ (d): (1) 63.8, (2) 71.9; NS (e): (1) 31.8, (2) 33.8; NS (f): (1) <1, (2) 2; NS	Grade I No details of randomisation other than 1:2 ratio randomisation No details on fall out Patients receiving sevoflurane had higher levels of emergence excitement
Martin *et al.*, 1993,[150] USA RCT	(1) Inhaled isoflurane maintenance (n = 68) (20 Propofol (n = 75) N_2O: inducted with halothane Procedures: strabismus surgery, ENT, orchidopexy, inguinal herniorrhaphy Age: 1–7 years	(a) PACU (b) DSU (c) Vomiting at home (d) Airway problems (e) Length of time on DSU (min)	(a): (1) 5, (2) 0; $p < 0.05$ (b): (1) 15, (2) 8; NS (c): (1) 23, (2) 14; $p < 0.05$ (d): (1) 22, (2) 6; $p < 0.01$ (e): (1) 88, (2) 81; NS	Grade II–1a
Meretoja *et al.*, 1996,[151] Finland RCT	Inhaled maintenance and induction (1) Halothane (n = 60) (2) Sevoflurane (n = 60) N_2O: given Procedures: bronchoscopy, gastroscopy Age groups: 3–11 months, 1–5 years, 6–15 years	Time (min) to: (a) emergence (b) discharge (c) PONV	3–11 months (a): (1) 27, (2) 10.5 (b): (1) 48.5, (2) 34 (c): (1) 6, (2) 1; $p < 0.05$ 1–5 years (a): (1) 29.4, (2) 11 (b): (1) 47, (2) 32 6–15 years (a): (1) 18.5, (2) 12.5; $p < 0.05$ (b): (1) 64.5, (2) 32.8; $p < 0.05$	Grade I Time to discharge increased with halothane
Moore and Underwood, 1994,[152] UK RCT	(1) Propofol/O_2 (n = 40) (2) Halothane/N_2O (n = 40) Induction with propofol Procedures: dental Age: 3–12 years	No. of patients with: (a) apnoea (b) movement on stimulation (c) pain (d) vomiting (e) Time from end of surgery to discharge (min)	(a): (1) 4, (2) 9; NS (b): (1) 35, (2) 12; $p < 0.001$ (c): No significant differences (d): (1) 0, (2) 0 (e): (1) 46.12, (2) 44.63; NS	Grade I

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Naito *et al.*, 1991,[153] Japan RCT	(1) Halothane (n = 15) (2) Sevoflurane (n = 15) N_2O: given Procedures: pulsed-dye laser therapy for port-wine stain on face or neck Age: 1–7 years	Time (min) to: (a) induction (b) emergence (c) recovery (d) vomiting (e) agitation	(a): (1) 3.3, (2) 3.2; NS (b): (1) 9.5, (2) 4.3; $p < 0.01$ (c): (1) 137.4, (2) 90; $p < 0.01$ (d): (1) 2, (2) 1; NS (e): (1) 3, (2) 9; NS	Grade I No details on randomisation No record of time to discharge
Pandit *et al.*, 1995,[154] USA RCT	(1) N_2O (n = 30) (2) No N_2O (n = 30) Procedures: tonsillectomy/ adenoidectomy Age: 4–12 years	(a) PACU stay (b) Vomiting measures	No impact on PACU stay or any measure of vomiting	Grade I Limited outcome measures No details on randomisation
Piat *et al.*, 1994,[155] France RCT	(1) Halothane (n = 17) (2) Sevoflurane (n = 17) N_2O: given Procedures: hernia, orchidopexy, hypospadias Age: 9 months to 9 years	Time (min) to: (a) intubation (b) extubation (c) emergence (d) Aldrete score > 8	(a): (1) 6.1, (2) 5.6; NS (b): (1) 19.2, (2) 14.6; $p < 0.01$ (c): (1) 33.4, (2) 18.1; $p < 0.001$ (d): (1) 35.9, (2) 25.3; $p < 0.01$	Grade I No details on randomisation No record of time to discharge
Reimer *et al.*, 1993,[156] Canada RCT	(1) Thiopentone/halothane + N_2O (n = 25) (2) Propofol (n = 25) (3) Propofol + N_2O (n = 25) Procedures: strabismus surgery Age: 2–12 years	Time (min) to: (a) extubation (b) eye open (c) time to vomit (d) recovery (e) hospital discharge (f) vomiting (%)	(a): (1) 10, (2) 11, (3) 6; $p < 0.0005$ (b): (1) 32, (2) 26, (3) 14; $p < 0.0001$ (c): (1) 8, (2) 1, (3) 1; $p < 0.0017$ (d): (1) 65, (2) 70, (3) 64; NS (e): (1) 155, (2) 148, (3) 140; NS (f): (1) 48, (2) 28, (3) 42; NS	Grade I
Runcie *et al.*, 1993,[157] UK RCT	Comparison of induction methods (1) Thiopentone, 0–5 years (n = 29) (2) Thiopentone, 5–11 years (n = 21) (3) Propofol, 0–5 years (n = 27) (4) Propofol, 5–11 years (n = 26) Procedures: circumcision, hernia repair N_2O: given with isoflurane	Time (min) to: (a) eye opening (b) oral intake (c) discharge (d) sedation score No. of patients with: (e) pain (f) vomiting	(a): (1) 21, (2) 20, (3) 17, (4) 16; NS (b): (1) 15, (2) 21, (3) 5, (4) 16; NS (c): (1) 95, (2) 117, (3) 88, (4) 86; $p < 0.004$ between groups 2 and 4 (d): (1) 13, (2) 14, (3) 12, (4) 12; NS (e): (1) 1, (2) 3, (3) 4, (4) 2; NS (f): (1) 0, (2) 0, (3) 0, (4) 0; NS	Grade I

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Splinter *et al.*, 1995,[158] Canada RCT	(1) Halothane/N_2O (n = 158) (2) Halothane/no N_2O (n = 162) Procedures: myringotomy and tube insertion Age: 0.5–13 years	Vomiting in first 24 h after surgery	13% in both groups	Grade I
Sury *et al.*, 1996,[13] UK RCT	(1) Sevoflurane (n = 20) (2) Halothane (n = 20) N_2O: given Procedures: general, urological, plastic, orthopaedic Age: 6 months to 6 years	Time (min) to: (a) emergence (b) discharge from recovery (c) discharge home No. of patients with: (d) vomiting (e) nausea (f) Incidence of pain and need for pain relief	(a): (1) 7, (2) 15; p = 0.002 (b): (1) 12, (2) 19; $p < 0.01$ (c): (1) 129, (2) 124; NS (d): (1) 2, (2) 2; NS (e): (1) 1, (2) 0; NS (f): Higher in sevoflurane group; $p < 0.01$	Grade I
Uezono *et al.*, 2000,[159] Japan Crossover design	(1) Propofol (n = 8) (2) Sevoflurane (n = 8) Maintenance only N_2O: not given Procedures: eye examination under anaesthetic Age: 1–5 years	(a) Extubation (b) Eye opening (c) PACU (d) Agitation (e) Vomiting (f) Patient satisfaction score	(a): (1) 16, (2) 13; NS (b): (1) 32, (2) 19; $p < 0.05$ (c): (1) 43, (2) 29; $p < 0.01$ (d): (1) 0, (2) 6; $p < 0.05$ (e): (1) 0, (2) 2; NS (f): (1) 5, (2) 4; $p < 0.05$	Grade II–2a Small numbers of a non-painful procedure Clearly more rapid emergence with sevoflurane
Ved *et al.*, 1996,[160] USA RCT	(1) Halothane/halothane (n = 20) (2) Propofol/propofol (n = 20) (3) Halothane/propofol (n = 20) (4) Propofol/halothane (n = 20) N_2O: given Procedures: tonsillectomy/ adenoidectomy Age: 3–10 years	(a) Extubation (b) Eye opening (c) PACU (d) Vomiting < 6 h (e) Vomiting > 6 h	(a): (1) 74, (2) 60, (3) 73, (4) 68; $p < 0.2$ (b): (1) 12, (2) 6, (3) 10, (4) 12; $p < 0.0002$ (c): (1) 15, (2) 7, (3) 12, (4) 15; $p < 0.0001$ (d): (1) 9, (2) 2, (3) 3, (4) 5; $p < 0.05$ (e): (1) 4, (2) 3, (3) 4, (4) 4; p = 0.97	Group I Explain concept of true endpoints (= discharge times or admission rate). No group differences in these No details on randomisation

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Viitanen *et al.*, 1999,[161] Finland RCT	(1) Propofol/sevoflurane (n = 26) (2) Sevoflurane/sevoflurane (n = 26) N_2O: given Procedures: adenoidectomy Age: 1–3 years	Time (min) to: (a) extubation (b) drinking (c) discharge Patients with: (d) vomiting in hospital (%) (e) delirium in hospital (f) pain discomfort scale (g) vomiting postdischarge	(a): (1) 17, (2) 11; $p < 0.0002$ (b): (1) 64, (2) 41; $p < 0.05$ (c): (1) 75, (2) 70; NS (d): (1) 8, (2) 15; NS (e): (1) 19, (2) 38; NS (f): Higher in group 2; $p = 0.04$ (g): (1) 4, (2) 7; NS	Grade I
Viitanen *et al.*, 2000,[162] Finland RCT	(1) Halothane/sevoflurane (n = 40) (2) Induction and maintenance (n = 40) N_2O: given Procedures: adenoidectomy Age: 1–3 years	(a) Emergence (b) Aldrete score > 10 (c) Interaction (d) Vomiting (e) Delirium	(a): (1) 23, (2) 14; $p < 0.0001$ (b): (1) 23, (2) 13; $p < 0.001$ (c): (1) 35, (2) 23; $p < 0.001$ (d): (1) 12, (2) 5; $p < 0.05$ (e): No difference	Grade I More postoperative excitement with sevoflurane, but difference not statistically significant
Watcha *et al.*, 1991,[163] USA RCT	Induction with N_2O and halothane then maintained with: (1) Halothane, N_2O, droperidol (n = 30) (2) Propofol/propofol (n = 30) (3) Propofol/propofol, N_2O (n = 30) (4) Propofol/propofol, N_2O, droperidol (n = 30) N_2O: given in groups 1, 3 and 4 Procedures: strabismus surgery Age: 6 months to 12 years	Time (min) to: (a) extubation (b) eye opening (c) following commands (d) oral intake (e) ambulation (f) discharge	(a): (1) 14.7, (2) 9.4, (3) 9.5, (4) 9.6; $p < 0.05$ vs group 1 (b): (1) 38.4, (2) 25.7, (3) 33.4, (4) 25.9; NS (c): (1) 84, (2) 54, (3) 48, (4) 57; $p < 0.05$, group 3 vs group 1 (d): (1) 220, (2) 135, (3) 131, (4) 199; $p < 0.05$, groups 2 and 3 vs group 1 (e): (1) 247, (2) 175, (3) 190, (4) 218; $p < 0.05$, group 2 vs group 1 (f): (1) 357, (2) 279, (3) 313, (4) 342; $p < 0.05$, group 2 vs group 1, and group 2 vs group 4	Grade I No details on randomisation

continued

***TABLE 67* contd** *Summary of paediatric clinical outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence
Walker *et al.*, 1997,[164] Australia RCT	(1) Halothane (n = 26) (2) Sevoflurane (n = 24) N_2O: given Procedures: lower abdominal, genitourinary Age: 2–13 years	Time (min) to: (a) induction (b) emergence (c) Aldrete score > 8 (d) Pain discomfort scale % Patients with: (e) emergence excitement (f) vomiting in hospital (g) vomiting postdischarge	(a): (1) 2.85, (2) 3.34; NS (b): (1) 33.06, (2) 21.36; $p < 0.01$ (c): (1) 35, (2) 22.1; $p < 0.01$ (d): Higher in group 2 (e): (1) 38.5, (2) 54.2; NS (f): (1) 19.2, (2) 16.7; NS (g): (1) 4, (2) 2; NS	Grade I No statistics reported for vomiting Length of stay not reported
Weir *et al.*, 1993,[165] USA RCT	(1) Halothane induction (n = 39) (2) Halothane vs propofol (n = 39) Maintenance N_2O: given Procedures: strabismus surgery Age: 3–12 years	(a) Discharge (b) Nausea and vomiting (c) Vomiting alone (d) Total vomit	(a): (1) 119, (2) 109; NS (b): (1) 27, (2) 17; $p < 0.05$ (c): (1) 25, (2) 16; $p < 0.05$ (d): (1) 2.8, (2) 1.5; $p < 0.05$	Grade I No details on randomisation
Welborn *et al.*, 1996,[166] USA RCT	(1) Sevoflurane/sevoflurane (n = 20) (2) Halothane/sevoflurane (n = 20) (3) Halothane/halothane (n = 20) (4) Halothane/desflurane (n = 20) N_2O: given Procedures: myringotomy and tube insertion Age: 1–7 years	Time (min) to: (a) emergence (b) recovery (c) discharge Patients with: (d) pain (e) vomiting (f) excitement	(a): (1) 11, (2) 11, (3) 10, (4) 5.6; $p < 0.0001$ (faster recovery in group 4) (b): (1) 17, (2) 19, (3) 21, (4) 11; $p < 0.0001$ (faster recovery in group 4) (c): (1) 134, (2) 129, (3) 117, (4) 137; NS (d): (1) 19, (2) 19, (3) 19, (4) 19; NS (e): (1) 6, (2) 9, (3) 4, (4) 4; NS (f): (1) 1, (2) 3, (3) 5, (4) 4; $p < 0.008$ (increased incidence in group 4)	Grade I No emergence excitement with sevoflurane

DSU, day surgery unit; PACU, postanaesthesia care unit

Appendix 6

Adult patient-based outcomes studies

TABLE 68 *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Baker *et al.*, 1995,[167] UK Survey	150 patients undergoing varicose vein day surgery	SF-36, a generic quality of life questionnaire with eight domains	Preoperative overall health was similar to that of the general population. There was increased pain and reduced role function at 1-month postoperatively. Social function and health perception were not improved at 6-months postoperatively	This study used a validated questionnaire to assess quality of life	Used a generic quality of life instrument to assess the impact of varicose vein surgery. 41% of respondents did not complete all three questionnaires (pre-operative, 1 month, 6 months)
Biemans *et al.*, 1998,[168] The Netherlands Survey	Comparison of patient satisfaction after laparoscopic and conventional day-case inguinal hernia repair	Verbal Rating Score of post-operative pain and nausea	TAPP (laparoscopic correction) mean time 80 (50–120); two patients could not be discharged on same day (TAPP); all patients discharged on same day for Griffith's procedure. All patients were satisfied with pre-operative information. TAPP group experienced less pain ($p < 0.05$) but more nausea ($p < 0.05$). Convalescence in TAPP group shorter than in Griffith group ($p < 0.05$)	Number of patients in TAPP group with postoperative nausea was greater than in the Griffith group. Less postoperative pain after the laparoscopic technique	Grade IV survey. Unclear on type of questions asked Number of ambulatory surgical procedures is increasing; laparoscopic hernia repair as well as the conventional Griffith method can be performed as a day procedure
Black and Sanderson, 1993,[169] UK Survey	373 patients undergoing day surgery in four hospitals in 1990	Postoperative symptoms, complications, health and functional status, general satisfaction, satisfaction with specific aspects of care	50% response rate. Outcome and satisfaction related to sex, age, type of procedure. Dissatisfaction with: parking (30%), occupied on ward (15%), level of privacy (15%), information (15%), after-effects of anaesthetic (13%), pain control (12%)	Questionnaire developed for a national comparative database	Puts concerns about anaesthesia into context of overall process of day surgery

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Brandner *et al.*, 1997,[170] UK RCT	Varicose vein surgery (1) TIVA (36 patients) (2) Propofol induction followed by inhalational anaesthesia with N_2 and isoflurane (37 patients) (3) Thiopentone induction followed by inhalational anaesthesia with N_2O and isoflurane (39 patients)	(1) Preoperative anxiety score (VAS) (2) Hall and van der Castle emotion scale (3) Bodily and biological states (Zancy) (4) Ben-Horin's overt sexuality scale	More dreaming in TIVA group than in thiopentone induction group ($p = 0.01$). TIVA group felt more sick ($p < 0.0038$) and felt happy ($p < 0.0038$)	No difference in sexual content of dreams; slight significance ($p < 0.0038$) of less sick and more happy states with those receiving TIVA. Conclude that propofol did not induce sexual behaviour or hallucinations when compared to thiopentone	Grade I Study conformed to checklist Validity of emotion scale validated by other authors Conclusions correct
Chung *et al.*, 1996,[171] Canada Telephone survey	1017 patients undergoing ambulatory surgery in a Toronto hospital	Postoperative symptoms and return to daily living function	76% response rate (778/1017). Incisional pain was most frequently reported (27%), followed by headache and drowsiness (12%). PONV was reported by 7%. Incidence of postoperative pain and PONV was higher in patients undergoing laparoscopy, orthopaedic and general surgery rather than eye surgery or D&C	Postoperative pain, nausea/vomiting, drowsiness, dizziness, headache are the most frequent postoperative symptoms. The type of surgical procedure did influence the type of postoperative symptoms	Grade IV Good response rate in a relatively large group
Cripps and Bevan, 1996,[172] UK Audit: questionnaire survey	Patient satisfaction in day surgery (3000 replies)	Questionnaire: choice of four faces (happiest; not so happy; slightly unhappy; very unhappy)	74% acceptable pain levels; 4% patients dissatisfied with perioperative information; 86% not upset by nausea and vomiting; 12% found it discomforting	Found patients satisfied with information; 25% of patients' pain levels were unacceptable	Grade IV Audit: questionnaire survey Large group
De Amici *et al.*, 2000,[173] Italy RCT	Influence of 'being under observation' on patients' psychological well-being; acceptability of locoregional anaesthesia	(1) GHQ before randomisation (2) Primary endpoint: Italian version of GHQ (3) Postoperative pain, nausea, headache (VAS)	Median baseline GHQ score computed as 1 (IQR, 0 to 4.5) in routine information group and 2 (IQR, 0 to 5) in the additional information group preoperatively	Study indicates that given the same information about anaesthesia and its undesired effects, interest as a result of inclusion in a research project has positive psychological and physiological consequences for patients	Grade II–1b Unclear about method of randomisation; size of effect is small. Preliminary findings only. Study shows that patients scheduled for surgery may change their behaviour simply because of being the subject of particular interest and attention

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Elliott *et al.*, 2000,[33] UK Descriptive study	Pilot study (40 women)	Willingness to pay	73% preferred propofol for induction. Willingness-to-pay values, mean of £208 for propofol and £105 for sevoflurane. 100% preferred propofol for maintenance, with a mean willingness to pay of £157. 85% of respondents understood what they were being asked to value	Pilot study to develop willingness to pay scenarios for use in an RCT	Grade IV; pilot study only
Enlund *et al.*, 1996,[174] Sweden RCT	Termination of pregnancy (1) Propofol + alfentanil (20 patients) (2) Thiopental + N_2O (19 patients)	Time for patient to be fully recovered; sick leave	Sick leave (0–2 days): PA group 19/20 patients, TN group 13/19 patients; $p < 0.05$. Mean difference in sick leave per patient between groups was 0.8 days	Study indicated a potential gain in costs of changing from thiopental + N_2O to propofol-alfentanil anaesthesia	Grade I Small groups. Premedication could have contributed to delayed recovery
Fenton-Lee *et al.*, 1994,[175] UK Audit	Assess patient acceptability and outcome of day surgery before and after changes to surgery	Interview at 1, 7 and 30 days Patient acceptability assessed using NHS questionnaire	No statistical tests performed. See conclusions	High level of patient satisfaction with service, pain control, anaesthesia, patient information, medical and nursing care and ward privacy. Reduction in wound complication rate occurred in the second 6 months when operations were performed by SpR as compared to SHO. Wound infection rate was used as a measure of the quality of surgery performed	Audit. Management of postoperative pain after day surgery still presents a challenge; patient satisfaction high; no statistical tests performed
Gan *et al*, 2001,[176] USA Descriptive study	Patients' willingness to pay to avoid PONV (n = 80)	Interactive computer questionnaire	Patients were willing to pay US $56 (US $26–97) for an anti-emetic that would completely prevent PONV. Patients who developed nausea (26%) and vomiting (11%) were willing to pay US $73 (US $44–110) and US $100 (US $61–200) respectively	Patients associated a value with the avoidance of PONV	Grade IV Survey More information on the methodological development of the survey instrument required
Ghosh and Kershaw, 1991,[177] UK Audit	Patients' feelings and satisfaction on having day surgery	Questionnaire survey	87.3% of GPs felt that an increasing number of patients treated on a day-care basis would result in stretching their own district and community nurses. 79.36% of GPs were willing to see more patients requiring a basket of 20 procedures treated in day surgery	Information about patients' attitudes towards day surgery. Patients felt day surgery had advantages over inpatient treatment. Areas of concern were: adequate postoperative pain relief and proper nursing/medical care at home	Audit. Provided information about patients' attitudes towards day surgery

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Ghosh and Sallam, 1994,[178] UK Descriptive survey	Patient satisfaction following day surgery (953/557 (58.4%))	Self-administered questionnaire (rating: area for concern; borderline; reserved satisfaction; first class)	Patient satisfaction: 52% were impressed by first class service at their outpatient visit; 6% were concerned; 62% felt that the information given was first class compared with 8% who were concerned. 2.5% contacted the hospital 24 h after their operation; 4.3% contacted their GP	Patients are satisfied with their treatment; contact with GP due to problems with pain management. Day surgery provides satisfaction for the majority of patients; does not produce undue extra demands on community services	Grade IV. Higher response rate; difficult to assess questionnaire, as it is not stated how the questions were asked
Gnanalingham and Budhoo, 1998,[179] UK Questionnaire survey	Hernia repair under local vs general anaesthesia Patients' willingness to have day-case hernia repairs under local or general anaesthesia	Interview either at hospital or by telephone	91% of patients fit for local or general anaesthesia preferred day surgery; 20% had no preference for type of anaesthesia; 33% had a strong preference for local anaesthesia; 47% had a strong preference for general anaesthesia. Preference for general anaesthesia associated with previous adverse experiences with local anaesthesia and an 'assumed feeling of anxiety' if awake during surgery	A small minority of patients preferred day case hernia surgery; there was a greater preference for general anaesthesia as the mode of anaesthesia. Authors felt that local anaesthesia is desirable and anxiety of patients regarding local anaesthesia should be reduced for a greater acceptability	Grade IV Patients interviewed preferred general anaesthesia (47%). 91% of patients preferred day-case hernia repair. Patients were young in comparison to those opting for inpatient surgery ($p < 0.05$)
Gupta *et al*., 1995,[78] Sweden RCT	Arthroscopy (1) Propofol (24 patients) (2) Isoflurane in O_2 (26 patients)	(1) Trieger Dot Test (2) P-deletion test (modified version, Sweden, found not to be sensitive enough) (3) Mood (MACL) (4) VAS pain scores	Surgery was longer the in propofol group than the isoflurane group ($p < 0.05$); no significant difference between groups in the six variables studied or in total mood score. Incidence of nausea and vomiting was 15% in isoflurane group and 4% in propofol group	P-deletion test not sensitive enough; Trieger Dot Test was sensitive, but interpretation was subjective. There was no difference in early recovery following anaesthesia with propofol or isoflurane. Psychomotor recovery was quicker following isoflurane anaesthesia. Discharge times were similar in the two groups	Grade I Double-blind; the two outcome measures (P-deletion test and Trieger Dot Test) were not suitable. Due to surgery being longer in the propofol group, the dose of alfentanil administered was greater. No difference in early recovery following anaesthesia with propofol or isoflurane
Gupta *et al*., 1996,[79] Sweden RCT	(1) Propofol induction; maintained with desflurane in O_2 and N_2O (25 patients) (2) Propofol induction; maintained with isoflurane in O_2 and N_2O (25 patients)	(1) Finger Tapping Test (2) Perception (PAT) (3) Mood (MACL)	Mood: calmness $p < 0.05$ isoflurane vs desflurane; Finger Tapping Test, no changes in baseline values in desflurane group; in isoflurane group there was significant impairment at 30 and 60 min	Desflurane is a useful alternative to isoflurane, but offers no clear advantage when used for maintenance of anaesthesia for operations of short duration	Grade I Unblinded; small groups; no difference in psychomotor recovery using PAT and Finger Tapping Test. The VAS for mood was not validated (translated from English to Swedish)

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Harju, 1991,[180] Finland Postal survey	Examination of patient satisfaction with hospital services among patients treated in day surgery	Postal survey; type of questions asked unclear	Before treatment: patient satisfaction 74%, indifferent 4%, negative 6%, 16% did not answer question. Satisfaction improved among those patients who had negative/ indifferent or no opinion at all before treatment	Day surgery has had a positive effect on surgical patient satisfaction; an important improvement was increased surgical availability	Grade IV Survey Availability of surgery influenced patient satisfaction; preferred waiting time 8–10 weeks. Unclear; 3 months prior to surgery, but must have surveyed patients after operation
Hawksworth, 1996,[21] UK Descriptive study	Pilot study: (18 anaes-thetists, 9 ODAs; 8 recovery nurses)	Willingness to pay	No definite difference could be shown in willingness-to-pay valuations of the benefits described, except in those participants who had not had a general anaesthetic. Anaesthetists and ODAs placed a higher value on effective anti-emesis, while recovery nurses did not	Pilot study. Authors felt that it would be feasible to do a similar study on day-surgery patients. Three ethics committees rejected the study on the grounds that the willingness-to-pay technique was too sensitive politically	Grade IV Pilot study only Willingness-to-pay values are arbitrary
Hunter *et al.*, 1998,[181] UK Descriptive study	Incidence of problems such as pain, head-ache, nausea and or vomiting. Effectiveness of self-medication in day patients 24 h after anaesthesia (553/635 patients (87%))	Self-administered questionnaire	Enflurane: increase in nausea and vomiting and pain ($p < 0.01$). Droperidol: increase in pain ($p < 0.05$) 52.3% experienced symptoms relating to the operation; 33.3% self-administered simple analgesics; 80.9% felt this was adequate; 5.6% who were concerned following day surgery sought GP advice; 2.2% visited their GP. 47% of respondents judged their immediate postoperative care to be worse than expected, 8% judged it to be better	Minor morbidity after day surgery is common; 40% developed pain after discharge, which reflects the short-acting nature of opioid analgesics. Scope for improvement in area of anti-emesis and postoperative analgesia	Grade IV Descriptive survey, showing scope for improvement in area of anti-emesis and postoperative analgesia

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Jakobsson *et al*., 1993,[182] Sweden RCT	Termination of pregnancy (1) Propofol in combination with ketamine 20 mg (50 patients) (2) Propofol in combination with fentanyl 0.1 mg (50 patients) (3) Thiopentone in combination with fentanyl 0.1 mg (50 patients) (4) Metho-hexitone in combination with fentanyl 0.1 mg (50 patients)	Self-administered questionnaire about memories of operation, dreams, pain, emesis and experiences during recovery period	Mean ± SD time to discharge: (1) 93 ± 31, (2) 96 ± 37, (3) 118 ± 61 ($p < 0.05$), (4) 108 ± 33 Pain: (1) 4, (2) 24, (3) 6, (4) 13; $p < 0.05$ Dreams: significantly ($p < 0.01$) more in group 1 (29 patients), than groups 2 (11), 3 (7) or 4 (4)	The combination of propofol and ketamine created a high incidence of dreams during anaesthesia. Concluded that propofol in combination with fentanyl is superior to the other three combinations	Grade I Unblinded Unsure of outcome measures used Overall incidence is low; highest frequency of patients complaining of postoperative pain was with propofol + ketamine Incidence of vomiting/ nausea was low
Kangas-Saarela *et al*., 1999,[183] Finland Prospective survey	Patients' experiences of day surgery; assessment of quality of care and patients' overall satisfaction with day surgery	(1) Nausea, 11-point rating scale (2) Pain intensity, 11-point rating scale (3) Use of pain medication (4) Satisfaction expressed as dissatisfied, fairly pleased, or very pleased	203 patients completed the survey; 11.3% (23.3 after general and 6.8% after spinal anaesthesia) had experienced nausea either at hospital or at home; at interview, 31% had no pain, 90% were pleased with day surgery, 10% were fairly pleased	Number of unexpected hospital admissions was higher at 4.6%; 24 h after discharge, most patients pleased and fairly well. Occurrence of nausea and vomiting was low. Overall incidence of complications and patient satisfaction was independent of type of anaesthesia	Grade IV Survey High admission rate warrants further evaluation. Outcome measures used were satisfactory
Klock *et al*., 2000,[184] USA Survey; abstract only	Evaluation of postoperative satisfaction instrument in a diverse patient population	Postoperative satisfaction instrument	217 responses out of 330 patients. Ratings of written comments showed significant differences in the numerical scores for overall satisfaction and each of the subscales ($p < 0.001$)	Instrument has proven reliability and validity	Abstract only: unable to see clearly when postoperative instrument can be used in other surgical specialties

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***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Larsen *et al.*, 1992,[89] Sweden Two-part study: I, experiment on outcome measures; II, RCT	(1) Propofol induction, propofol + O_2 maintenance (15 patients) (2) Propofol induction, isoflurane 5–2% maintenance (15 patients) (3) Control group: 15 unanaesthetised volunteers	PAT	Significant difference ($p < 0.05$) in psychomotor recovery of PAT between propofol group and control group; no significant difference in psychomotor recovery on PAT between isoflurane and control; change in choice reaction time – difference between isoflurane ($p < 0.05$) and propofol ($p < 0.01$) groups compared with control in PAT-60	Found that PAT has the following features: (1) shallow learning curve; (2) consistent and reproducible; (3) phenomenon of 'arousal' has not been noticed; (4) simple and easy to use. Found, using this PAT, that psychomotor recovery following isoflurane anaesthesia is quicker than that following propofol infusion	Part II is grade I; Part 1 is experimenting with PAT If the PAT is validated and reliable, it has shown that psychomotor recovery following isoflurane anaesthesia is quicker than that following propofol infusion. Further studies are required to evaluate the precise difference between PAT-60 and PAT-200
Law, 1997,[185] UK Descriptive study (telephone survey audit)	(1) Assess usefulness of preoperative assessment (2) Identify written and verbal advice (3) Identify usefulness of counselling criteria (4) Assess patient satisfaction 45 patients approached, 38 participated (84.4%)	Telephone survey No real outcome measures of quality of life measures used Rating: poor, fair, satisfactory, excellent	Nursing care: excellent 76.3%; satisfactory 23.6%. Advice leaflets: excellent 57.8%, satisfactory 42.1%. Doctor waiting times 5–180 min; 50% waited 30 min; mean waiting time 56.97 min (median 30 min). 26.3% (10) said they would prefer a longer stay in hospital	Patients on hold were happy with new day-surgery service; allocation of preoperative assessment time should be realistic	Grade IV Patient satisfaction was difficult to measure; questions on patient satisfaction were closed questions with a rating of poor, fair, etc. Sample size was small
Leith *et al.*, 1994,[19] England and Wales Descriptive survey	Questionnaire survey looking at: (1) use of analgesics postoperatively (2) use of prophylactic anti-emetics 231 units; 147 replied (64%)	Questions only	97.8% used NSAIDs; most using diclofenac; 61.7% using ketorolac, administered either i.m. or i.v. 90.8% supplied patients with analgesic drugs to take home. 53.9% gave prophylactic anti-emetic drugs: metoclopramide 46.1%; ondansetron 9.2%; droperiodol 28.4%; prochlorperazine 17.7%. Pain was considered a problem in 69.5%; 44% felt nausea was a problem	Pain problems are a cause for concern in about 70% of units. The authors believe that droperidol should not be used in day surgery. Prophylactic anti-emetic drugs were given in 53.9% of units	Grade IV Questionnaire survey Looking at practices in different day-surgery units

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Luntz *et al.*, 2000,[195] Germany Comparative study; abstract only	(1) TIVA with propofol (2) Propofol for induction and sevoflurane for maintenance (3) Sevoflurane for induction and maintenance	Aldrete score (time of recovery); mean arterial blood pressure; incidence of postoperative shivering, pain (VAS) and nausea	Nausea was significantly more severe in group 3 at 30 and 60 min; for both group 1 and 2 –120 min vs group 1 No difference with regard to shivering 24 h after surgery. 50% of group 3 patients complained of discomfort associated with induction of anaesthesia ($p < 0.05$)	Inhalation induction of anaesthesia with sevoflurane (group 3) was associated with a lower incidence of hypotension; following anaesthesia induction in the elderly, some patients complained on discomfort Group 1 was similar with regard to patient comfort and recovery	Abstract only Unclear how patient satisfaction was measured or what questions were asked at the 24 h interview. Unable to draw any conclusions without full study design details
Macario *et al.*, 1999,[186] USA Survey	Quantification of patients' preferences for postoperative anaesthesia outcomes	Rank postoperative outcomes from most undesirable to least undesirable	52% response rate. Vomiting was the least desirable outcome by both ranking methodology and relative value methodology. Previous experience with a certain anaesthesia outcome was not related to a patient's ranking of outcomes	Variability in how patients rated post-operative outcomes. Avoiding nausea/vomiting, incisional pain, gagging on the endotracheal tube was a high priority for most patients	Grade IV Survey Provided an indication of patients' relative preferences for anaesthesia outcomes. Variability in patient preferences, but avoiding PONV was a high priority
Myles *et al.*, 2000,[187] Australia Observational study	To develop a valid, reliable and responsive measure of the quality of recovery after anaesthesia	(1) Preoperative data: nine items rated, then status on a three-point scale to give quality of recovery score (2) 40-item questionnaire with items on a five-point Likert scale (QoR-40) (3) Details of surgery (4) Postoperative recovery (VAS)	Found good convergent validity between QoR-40 and VAS scores ($\rho = 0.68$; $p < 0.001$). Construct validity was by a negative correlation with duration of hospital stay ($\rho = -0.24$; $p < 0.001$) and a lower mean. Good test–retest reliability. QoR-40 was completed in less than 6.3 (SD 4.9) min	Developed and evaluated 40-item quality of recovery score (QoR-40) in a diverse group of patients recovering from many types of surgery. Validity, reliability and clinical acceptability of score excellent	Testing the validity and reliability of a recovery score to determine the quality of recovery after anaesthesia and surgery
Myles *et al.*, 2000,[188] Australia Survey	Identify potentially modifiable factors associated with dissatisfaction	Rates of satisfaction: satisfied, somewhat dissatisfied, dissatisfied	10,811 patients were reviewed on the day after surgery to rate their satisfaction with care; satisfaction level was 96.8% and 2.3% were somewhat dissatisfied. Patients who were dissatisfied were generally younger and had a longer duration of anaesthesia. Factors associated with patient dissatisfaction were postoperative pain, nausea, vomiting and other complications	There was a high rate of patient satisfaction within anaesthesia. Factors strongly associated with satisfaction included old patient age, male sex, measures of increased perioperative risk	Grade IV Survey The high rate of patient satisfaction may be an under-representation of the true level of dissatisfaction. A large survey of surgical patients. Minor post-operative complications are important to patients

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Nelskyla, 1997,[190] Finland RCT	(1) Isoflurane + N_2O (30 patients) (2) Propofol + N_2O (30 patients) 57/60 returned the questionnaire	DSST Return to daily activities Pain and nausea (pain measured on a VAS)	Early recovery was faster in the isoflurane group ($p < 0.05$); recovery assessed by the DSST showed no difference; no patient in either group had returned to their preanaesthesia level at the 60 min time point	Concluded that isoflurane and propofol are suitable anaesthetics for laparoscopic hysterectomy. Early recovery was faster in the isoflurane group. Laparoscopic hysterectomy is not yet a suitable procedure for day surgery	Grade I Double-blind; small sample Faster wakening from isoflurane; no major differences noted between isoflurane and propofol
Nkyekyer, 1997,[190] Ghana Survey	Determined the acceptability to patients of various aspects of day-case laparoscopy. Determined sources of morbidity. Identified ways in which the service could be made more acceptable to patients	Interviews covering information, waiting periods, symptoms, etc.	29% of patients indicated that they had not had adequate explanation about their operation; 15% felt the reporting time was too early; 24% preferred being sent to theatre one patient at a time; 61% saw unconscious patients in the theatre waiting area; 52% would have preferred overnight stays; 14% felt pain during their operation	To make day-case laparoscopy more acceptable, a dedicated day-surgery unit with formal anaesthetic cover should be established. Stricter criteria should be established for patient discharge and, where appropriate, patients should be given the option to stay overnight	Grade IV Survey Unclear how the questionnaire was administered or how patient satisfaction was measured. Half of patients did not feel well enough to go home. Problems in care/management were identified
Otte, 1996,[191] UK Descriptive study	ENT day surgery: examined patients' experiences and views of day surgery (8 patients)	Grounded theory methodology Validity: peers independently reviewed the substantive codes and categorising process. Reliability: allowed another researcher to replicate research	Four theoretical constructs emerged: (1) the importance of planning; (2) the fear of the unknown; (3) improving the service; (4) the value of day surgery Inadequate scheduling of operation; inadequately prepared for day surgery in terms of information and education; breakdown in communications during their clinical encounter	Patients expressed dissatisfaction with the scheduling of their operations; patients felt they were inadequately prepared for day surgery in terms of information and educational support	Qualitative study Only 8 participants. Methodologically sound for qualitative approach
Philip *et al.*, 1996,[108] USA RCT	(1) Sevoflurane (149 patients) (2) Isoflurane (97 patients)	VAS baseline assessment of mental state Psychomotor function (DSST) Aldrete recovery score (validated)	Groups were similar. Significantly more sevoflurane patients were able to complete each component of the VAS at 15–60 min. More sevoflurane patients were able to complete the DSST at 15–60 min. The Aldrete score was used to assess recovery while in the PACU: 95% of sevoflurane and 81% of isoflurane group met the Aldrete recovery criteria (score > 8) ($p = 0.004$). The level of consciousness was significantly higher for the sevoflurane patients at admission and 15 min into recovery ($p < 0.001$)	Patients who received sevoflurane instead of isoflurane with N_2O for maintenance emerged more rapidly from ambulatory anaesthetic. Times to eye opening, command response, orientation and ability to sit without nausea and/or dizziness were significantly faster after sevoflurane. Significantly more sevoflurane patients (95% vs 81%) met phase 1 of the postanaesthesia Aldrete recovery criteria (score > 8) at arrival. More sevoflurane patients were able to complete psychomotor recovery tests during first 60 min postanaesthesia	Grade I Multicentre RCT No blinding, but validated outcome measures. Sevoflurane is a useful inhaled anaesthetic for maintenance of ambulatory anaesthesia

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Ratcliff *et al*, 1994,[192] UK Audit	Incidence of PONV, pain levels, overnight admission, patient satisfaction with day surgery (laparoscopy or sterilisation) (72 patients)	Duration of anaesthesia Time to eye opening; time to discharge Postal questionnaire Self-assessment pain-intensity scale	Incidence of emetic symptoms: 4.2% had PONV at more than one assessment while in the day unit. No significant differences between groups for nausea, vomiting or administration of antiemetics. Morbidity: 70% of patients were still not feeling normal after 2 days. 7.7% would prefer to stay overnight	Changes in anaesthetic practice would seem to make day-case laparoscopy a more acceptable procedure than previously reported	Audit No significant differences between groups after discharge Nausea, nausea and vomiting and pain scores were lower than reported in other studies
Rhodes, 1991,[193] UK Audit	Determine current anaesthetic practice for cataract day patients; assess extent of morbidity experienced by patients at home	Surgical outcome and frequency of follow-up; questionnaire; VAS pain score during insertion of local anaesthetic block and intraoperatively	Mean pain scores for insertion of local anaesthetic blocks: no significant difference between day patients or inpatient groups; 47% patients reported intraoperative discomfort on operating table. Overnight complications: 47% day patients; 37.5% inpatients. No significant difference between groups	Day-care cataract extraction is acceptable to patients. Morbidity in 47%: minor and self-treated. No significant difference from the inpatient group in either anaesthetic or surgical complications. No clear advantage between local anaesthesia alone or additional sedation was demonstrated	Grade IV Survey design Authors give a summary of the questionnaire used. Day-care cataract extraction was acceptable to patients. Half of patients experienced complications at home overnight
Rudkin *et al*., 1996,[194] Australia Pilot study: prospective study	Review of the influence of differently organised facilities on patient outcome; common trends and differences in eight Australian day-surgery facilities	Preoperative waiting time; time in recovery room; complications; follow-up information on patient satisfaction	Longer patient waiting time in hospital-integrated facilities using inpatient mixed recovery room care (144.9 min; median 125); dedicated day recovery 102.8 min (median 95); free-standing 72.5 min (median 60.5)	Impact of different day-surgery facility types on efficiency in day-surgery care delivered 5% patients reported that information given about anaesthesia was poor; 99% patients reported that they had received good or satisfactory information	Pilot study only: reviewed 3 types of day facility; shown to have differing effects on management efficiencies and patient satisfaction
Tong *et al*., 1997,[196] Canada Prospective survey	Hypothesised that satisfaction with anaesthesia was a predictor of global satisfaction with ambulatory surgery and that 24 h postoperative symptoms were a predictor of satisfaction with anaesthesia	Postanaesthesia discharge scoring system Preoperative data	5228 patients studied. Telephone interviews with 52%. Global dissatisfaction: 2.5% would decline to return to the same unit; presence of postoperative symptoms, increased dissatisfaction. Variables associated with global dissatisfaction (68/2730): 18 had personal preference for inpatient care; 3 had adverse outcomes; 6 had postoperative symptoms	Dissatisfaction with anaesthesia is a predictor of global dissatisfaction with ambulatory surgery. An increased number of symptoms 24 h after operation is a predictor of dissatisfaction with anaesthesia. The rate, however, is low	Grade IV Survey The predictors from this study need to be validated by a second data set from another centre. However, the validity of the questions was established in a previous study The rate of global dissatisfaction and dissatisfaction with anaesthesia was found to be low

continued

***TABLE 68* contd** *Summary of adult patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments
Tzabar *et al.*, 1996,[197] UK Comparative study	General anaesthesia (54 patients) vs local anaesthesia (30 patients)	Cognitive failure questionnaires: 25 questions about lapses 3 days before admission and 3 days after discharge	Mean preanaesthetic score: general anaesthesia, 35.2 ($p < 0.01$); local anaesthesia, 33 Mean postanaesthetic score: general anaesthesia, 38.6; local anaesthesia, 31 (NS)	Cognitive failure questionnaire. In a 3-day period after discharge, patients undergoing general anaesthesia experienced a significant increase in cognitive failures relating to preoperative baseline scores and to patients who underwent local anaesthesia	Grade IV Duration of impairment could not be assessed; procedures were not equal between general anaesthesia and local anaesthesia; bias of non responders
Winwood, 1993,[198] UK RCT	Propofol induction (25 patients) Thiopentone induction (25 patients)	Anxiety assessed 1 h before induction and at 30 min and 1, 2 and 4 h postoperatively on STAI	Preoperative STAI: propofol, 36.64; thiopentone, 37.56 (NS) Postoperative 30 min STAI: propofol, 28.68; thiopentone, 36.88 ($p < 0.0002$) Postoperative 1 h STAI: propofol, 25.44; thiopentone, 36.44 ($p < 0.0001$) Postoperative 2 h STAI: propofol, 25.40; thiopentone, 34.40 ($p < 0.0006$) Postoperative 4 h STAI: propofol, 26.40; thiopentone, 34.72 ($p < 0.0007$)	Propofol produced statistically lower levels of anxiety when compared with thiopentone	Grade 1. Single blind. Small numbers

IQR, interquartile range; ODU, operating department assistant; PACU, postanaesthesia care unit; SHO, senior house officer; SpR, specialist registrar

Appendix 7

Paediatric patient-based outcomes studies

TABLE 69 *Summary of paediatric patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments (grade of evidence and checklist criteria)
Grenier *et al.*, 1994,[199] France Clinical audit	Assessment of the home recovery and comfort of children who had undergone day procedures	Pre- and postoperative assessment Postal questionnaire returned by parents	25% suffered pain; 2/3 related to surgical wound, 1/3 to headache; pain more frequent at home (41% vs 15%, $p < 0.05$)	Peri- or postoperative respiratory events were rare; the children were premedicated more frequently (95%) then is usually reported; Patients did not receive a systematic prescription of analgesics to cover their home needs; good satisfaction rate (95%)	Clinical audit only; able to look at quality of home recovery. Two major insufficiencies, analgesia and pain at home, were more frequent
Jolliffe, 1997,[200] UK Survey	142 patients (93 parents responded) aged 0–15 years Procedures: ENT, dental, general, orthopaedic	Incidence of postoperative problems Symptoms at home Assessment of appropriateness of length of stay	Children were not upset by day surgery, 25% were upset by changing into a theatre gown. 53% and 10% reported pain and PONV after discharge, respectively	Parents reported only minor problems postdischarge	Grade IV
Kotiniemi *et al.*, 1996,[201] Finland Survey	Children attending for day surgery: 40 day patients vs 45 inpatients	PHBQ: patients filled in the questionnaire 1 day, 1 week and 1 month after discharge	No behavioural changes in 20 (23%) children; problematic changes seen in 52 (61%); behavioural improvements in 28 (33%); problematic changes detected in 73% of day-case children and 46% of the inpatient group. Behavioural problems in children aged 3–7 years: 68% in day-case group; 46% in inpatient group (95% CI for difference, –6 to 51)	Number of behavioural changes after both day-case and inpatient ENT operations in 2–10 year old children. Behavioural problems were equally common after day-case and inpatient treatment	Grade IV Descriptive survey

continued

***TABLE 69* contd** *Summary of paediatric patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments (grade of evidence and checklist criteria)
Kotiniemi *et al.*, 1996,[201] Finland RCT	Intravenous thiopentone (29 patients) Inhalational halothane (28 patients) Rectal methohexitone (29 patients)	PHBQ: parents evaluated changes in their child's behaviour at 1 day, 1 week and 1 month	Problematic changes were detected in 17 (59%) children receiving thiopentone, 14 (50%) children receiving halothane and 17 (58%) children receiving methohexitone (NS) There were no statistically significant differences between the groups in the proportion of children who showed postoperative behavioural problems	Children who received halothane behaved more calmly, but had significantly more negative memories of the induction of anaesthesia (halothane group, 6 children; thiopentone group, 2; methohexitone group, 1)	Grade I Small numbers; problematic changes not significant
Kotiniemi *et al.*, 1997,[202] Finland Descriptive study	Evaluation of type and occurrence of changes in children's behaviour during the first 4 weeks after day surgery	Preoperative questionnaire was adapted from the PHBQ PHBQ carried out post-operatively; behaviour assessed using a 4-point scale	There were no problems in cooperation in 423 (81%) subjects during premedication and in 323 (61%) during anaesthetic induction. There were more problematic changes at day 0 ($p < 0.001$), while the difference at week 4 was not significant ($p = 0.9$). Pain was the only postoperative symptom mentioned in the questionnaire that significantly affected the occurrence of behaviour changes	Age of child, pain at home and previous difficult experience of healthcare were predictors of problematic behavioural changes at home. Gender and previous operations did not have a significant effect on incidence of changes. The results emphasise the importance of the effective prevention of postoperative pain. It is important to avoid unpleasant experiences in all contacts that children have with healthcare	Grade IV Descriptive survey; not a randomised comparison, so no conclusions can be drawn about different anaesthetic techniques Behaviour changes are seen in children who have mild pain at home and severe pain plus a previous bad experience of healthcare which has adversely affected the attitude of the child towards doctors or nurses
Payne *et al.*, 1992,[203] South Africa RCT	Oral trimeprazine, methadone and droperidol (31 patients) Oral midazolam (30 patients) Intramuscular midazolam (31 patients) Controls (31 patients)	A posthospital behaviour questionnaire (not the PHBQ) on two publications. Assesses behaviour changes in six categories	Changes in behaviour reported in 78% of subjects. Use of premedication showed little benefit. General anxiety – night crying was seen in 10 children receiving i.m. midazolam ($p < 0.05$), 39 receiving oral midazolam ($p < 0.05$), 20 controls and 16 receiving trimeprazine, methadone and droperidol	Midazolam premedication via the oral or i.m. routes provides benefit to a child in that some behavioural changes on returning home are decreased in frequency and severity. Pharmacological premedication alone is poor protection against a child's behavioural problems caused by a theatre experience	Grade I RCT, single blind No indication of how behaviour changes were assessed; difficult to assess whether the medication had an effect on a child's behaviour

continued

***TABLE 69* contd** *Summary of paediatric patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments (grade of evidence and checklist criteria)
Scaife and Campbell, 1988,[204] UK RCT	Day patients (34) vs inpatients (27) Children's behaviour	Five-point scale using various descriptors, derived from a standardised behaviour screening device. Parents rated their own subjective anxiety about different aspects	There were few significant differences in the magnitude or direction of change between the day-patient and inpatient groups; no significant differences were found between day patients and inpatients on the post-discharge ratings or at 3 months follow-up	The results show trends in favour of day procedures; the argument is made that day procedures should be the preferred option for minor surgery in young children	Grade I RCT, no blinding No significant changes in behaviour between day patients and inpatients. Difficult to draw a conclusion
Selby *et al.*, 1996,[205] UK Descriptive survey	266 children (aged 5 years and over) were interviewed by an anaesthetist about minor sequelae after day surgery. 10% of patients were interviewed	PONV, sore throat, visual disturbance, headache, shivering, bad dreams	PONV 53%, sore throat 31%, visual disturbance 25%, headache 19%, shivering 13%, bad dreams 4%	Personal interviews with children revealed a higher incidence of minor morbidity following day surgery than had been previously reported	Unrepresentative sample, as only 10% of the sample agreed to be interviewed. However, the results were significant
Sikich *et al.*, 1997,[206] Canada Survey	Evaluation of parental perceptions, expectations and preferences for post-anaesthetic recovery of children	Postal questionnaire	Extreme concern expressed for pain (45.5%). 28.7% had postoperative vomiting. Pain vs sleepiness, $p < 0.0001$; pain vs vomiting, $p < 0.02$	5% of parents expected their child to be active and alert in the first 24 h after surgery; 22.8% preferred quicker postanaesthetic recovery; speed of discharge was not a priority for parents; parents were concerned about postoperative pain and postoperative vomiting	Grade IV Survey design Unclear what questions were asked in the questionnaire
Tarbell *et al.*, 1992,[207] USA Observational study	Evaluation of the reliability and validity of the TPPPS	TPPPS and a VAS scale	Scores on the TPPPS were in the range 0–7. The variability in the TPPPS scores appears acceptable in spite of the negative skew, given that the surgical procedures evaluated were not the most painful procedures that a young child may undergo. Inter-rater reliability checks were conducted for 38% of children	The TPPPS was found to have satisfactory internal reliability. The inter-rater reliability was good, with κ values for pain behaviour items ranging from 0.53 to 0.78	Grade IV Observational study Further study is indicated to specifically control for analgesic factors that may have complicated the interpretation of the TPPPS scores (e.g. the sedative properties of analgesic medications)

continued

***TABLE 69* contd** *Summary of paediatric patient-based outcomes studies*

Study	Investigations and subjects	Outcome measures	Results	Conclusions and grade of evidence	Reviewers' comments (grade of evidence and checklist criteria)
Vernon *et al.*, 1966,[208] USA Descriptive study	General anxiety and regression; separation anxiety; anxiety about sleep; eating disturbance; aggression towards authority; apathy–withdrawal 387/800 (48%) of questionnaires were returned and useable	Posthospital behaviour questionnaire: parents compared their child's typical behaviour before hospitalisation with their behaviour during the first week after hospitalisation	Age, duration of hospitalisation and occupational status were significantly related to one or more types of responses. Gender, previous hospitalisation, degree of pain experienced during hospitalisation and birth order were unrelated to any type of response by any analysis	The combination of illness and hospitalisation is a psychologically upsetting experience for children in general, resulting in increased separation anxiety, increased sleep anxiety and increased aggression toward authority	Grade IV Descriptive study Satisfactory data. Looked at the hypothesis that children aged 6 months and 4 years are most likely to be upset following hospitalisation. Significant findings were associated with length of hospitalisation. High rate of non-responders (52%)
Westerling, 1999,[209] USA Prospective study	Evaluation of whether it is possible to quantitate postoperative pain and nausea by using the TAS in 50 children aged 4–12 years who were undergoing ophthalmic surgery	The TAS consists of nine bright red wooden balls Postoperative pain and nausea were evaluated by means of the TAS every hour, 3–4 times before discharge	Children understood the principle of the TAS; five children could not rate either nausea or pain at their first attempt postoperatively, due to distress or restlessness	The TAS is easy to explain to children and is easy to use. Ratings ranging from light discomfort to severe pain were made by 49 children; one child had no pain	Grade IV Further validation is needed of this tool for assessing postoperative pain and the efficacy of given treatments
Wilson and Doyle, 1996,[210] Canada Descriptive study	Assessment of the suitability of use by parents of three pain assessment scores commonly used in paediatric anaesthesia (40 children)	Pain scores: (1) objective pain score; (2) VAS; (3) four-point numerical scale	Objective pain scores, range 0 to 8; numerical scale scores, range 0–3; VAS scores, range 0–99. Correlation coefficients for parental and medical pain scores in recovery: objective pain scores, 0.77; four-point numerical scores, 0.70; VAS scores, 0.69. Correlation coefficients 1 h after leaving recovery area: objective pain scores, 0.81; four-point numerical scores, 0.80; VAS scores, 0.73 ($p < 0.01$). In 80 simultaneous observations of each kind made by an observer and the parents, 44 (55%) of the objective pain scores, 49 (61%) of the four-point numerical scores, and 42 (52.5%) of the VAS-scores were identical within 10 min	Study showed a high degree of correlation between the assessments performed simultaneously by an observer and the parent	Grade IV Parents are able to carry out pain assessments. Two types of surgical procedure were chosen: one where a regional block was used (i.e. where pain is minimal); one where a regional technique is unsuitable. Teaching of parents how to carry out pain assessments

Appendix 8

Characteristics of cost or economic comparisons of anaesthetic agents

TABLE 70 *Characteristics of cost or economic comparisons of anaesthetic agents*

Authors	Year of publication	Country of study	Type of study*	Alternatives compared	No. of subjects
Alhashemi *et al.*[29]	1997	Canada	Economic	Thiopentone/isoflurane Propofol/alfentanil Propofol/propofol	31 31 31
Churnside *et al.*[23]	1996	UK	Audit	Surgical procedures	175
Dexter and Tinker[40]	1995	USA	Cost	Cost impact of reducing adverse anaesthetic outcomes	1884
Enlund *et al.*[174]	1996	Sweden	Economic	Thiopentone Propofol	19 20
Fleischmann *et al.*[212]	1999	Austria	Cost–consequences	Sevoflurane, re-breathing bag Sevoflurane, circle system Propofol, i.v. bolus Thiopentone, i.v. bolus	20 20 20 20
Halberg *et al.*[213]	1996	USA	Cost	Propofol Isoflurane Desflurane	84 23 43
Heidvall *et al.*[28]	2000	Sweden	Economic	Propofol/sevoflurane Propofol/propofol + alfentanil Propofol/propofol + remifentanil	25 25 25
Hsu and Shalansky[214]	1995	Canada	Economic	Thiopentone Propofol	22 52
Jakobsson *et al.*[84]	1997	Sweden	Economic	Propofol maintenance Desflurane maintenance	40 40
Kain *et al.*[215]	1994	USA	Cost–consequences	Propofol Thiopentone/pentobarbitone	? ?
Killian *et al.*[86]	1992	Canada	Economic	Propofol TIVA Thiopentone/isoflurane	33 30
Kurpiers *et al.*[216]	1996	USA	Cost	Desflurane Propofol	27 26
Meyer-McCright *et al.*[217]	1998	USA	Cost	Thiopentone/isoflurane Propofol/isoflurane Propofol/desflurane	13 126 55
Nathan *et al.*[99]	1998	Canada	Economic	Sevoflurane Propofol	26 26
Patel *et al.*[218]	1996	USA	Effectiveness	Anaesthetic procedures, addition of desflurane to formulary	1568
Reis *et al.*[219]	1999	Canada	Cost–consequences	Isoflurane Sevoflurane	20 20
Rosenberg *et al.*[220]	1994	USA	Cost	Propofol Desflurane	25 25
Smith and Thwaites[125]	1999	UK	Cost–consequences	Sevoflurane Propofol	30 31

continued

***TABLE 70* contd** *Characteristics of cost or economic comparisons of anaesthetic agents*

Authors	Year of publication	Country of study	Type of study*	Alternatives compared	No. of subjects
Smith *et al.*[221]	1999	Multicentre: Belgium, France, The Netherlands, UK	Cost	Propofol TIVA Propofol/sevoflurane Sevoflurane/sevoflurane Thiopentone/isoflurane	72 70 69 22
Song *et al.*[126]	1998	USA	Effectiveness	Fast tracking vs standard care	120
Sun *et al.*[222]	1999	USA	Cost–consequences	Methohexitone/sevoflurane Methohexitone/desflurane Propofol/sevoflurane Propofol/desflurane	30 30 30 30
Tang *et al.*[129]	1999	USA	Economics	Propofol TIVA Propofol/sevoflurane Sevoflurane/sevoflurane	35 34 35
Wagner and O'Hara[223]	1995	USA	Cost	Propofol induction Thiopentone induction	103 140
Wagner and O'Hara[224]	1997	USA	Economic	Sevoflurane Isoflurane	25 22

* *Defined by author*

Appendix 9

Quality of cost or economic comparisons of anaesthetic agents

TABLE 71 *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Alhashemi *et al.*, 1997,[29] Canada	Source: RCT Randomisation: CGRNT Blind: single Power estimate: NK Inclusion/ exclusion criteria: 11 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetic and drugs, nursing time	Not stated	**Costs** Inhalational: US $36.4 ± 5.3* Balanced: US $66.5 ± 11.7* TIVA: US $86.0 ± 20.6* $p < 0.05$, different to each other **Effectiveness*** No differences
Churnside *et al.*, 1996,[23] UK	Audit	Study design: AD Cost data: ACCEPT Analysis: INAD Sensitivity analysis: no	Consumables Equipment Labour Overheads	List prices Salary costs Literature	Detailed median (range) costs estimated for day-surgery procedures and prespecified anaesthetic regimen
Dexter and Tinker, 1995,[40] USA	Source: descriptive, retrospective chart review, no controls	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: INAD Analysis: INAD	Total charges per inpatient episode, excludes physician fees	Charges	Eliminating adverse anaesthesia outcomes decreases total costs by 0–2%

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	Economic checklist		
Enlund *et al.*, 1996,[174] Sweden	Source: RCT Randomisation: sealed envelope Blind: single Power estimate: NK Inclusion/ exclusion criteria: NK Recruitment rates: 40/41 Representative sample: NK Comparable groups: NK	Study design: INAD Effectiveness data: good Outcome data: AD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics, sick leave	Anaesthesia not stated Sick leave: social insurance	**Costs** Excluding sick leave: thiopental, SEK 15 propofol, SEK 72 **Effectiveness*** Propofol associated with lower postdischarge recovery times
Fleischmann *et al.*, 1999,[212] Austria	Source: RCT Randomisation: NK Blind: single Power estimate: NK Inclusion/ exclusion criteria: 6 Recruitment rates: NK Representative sample: NK Comparable groups: NK	Study design: AD Effectiveness data: INAD Outcome data: NA Cost data: INAD Analysis: INAD Sensitivity analysis: no	Anaesthetics and drugs	US wholesale prices	**Costs** Thiopental: US $14.5 ± 9.5* Propofol: US $20.1 ± 7.8 Sevoflurane/circle: US $25.1 ± 12.1 Sevoflurane/bag: US $19.4 ± 18.1 $p < 0.05$ vs sevoflurane/ circle **Effectiveness*** No differences

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Halberg *et al.*, 1996,[213] USA	Source: cohort design Randomisation: no Blind: no Power estimate: no Inclusion/ exclusion criteria: 2 Recruitment rates: no Representative sample: no Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and anti-emetics	Hospital-specific drug costs	**Costs** Desflurane: total cost US $53.30 Isoflurane: total cost US $42.60 Propofol: total cost US $59.66 Statistical difference only between isoflurane and propofol **Effectiveness** Five time variables were significantly different: total anaesthesia; end of surgery to leave operating room; total length of stay; end of anaesthesia to discharge; incision to discharge
Heidvall *et al.*, 2000,[28] Sweden	Source: RCT Randomisation: envelope Blind: – Power estimate: NK Inclusion/ exclusion criteria: 6 Recruitment rates: NK Representative sample: NK Comparable groups: NK	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetic and drugs	Swedish pharmacopoeia	**Costs** Propofol/alfentanil: US $150.08 ± 18 Sevoflurane: US $122.61 ± 4.7 Propofol/remifentanil: US $166.08 ± 19.9 **Effectiveness*** No differences

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Hsu and Shalansky, 1995,[214] Canada	Source: prospective cohort Randomisation: no Blind: no Power estimate: yes. 14 patients per group estimated to detect a 15% difference in time to eye opening at 80% power Inclusion/ exclusion criteria: 4 Recruitment rates: NK Representative sample: NK Comparable groups: NK	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics	Not known	**Costs** (anaesthetic acquisition only) Thiopental: US $8079.68 Propofol: US $60331.28 per year for the institution **Effectiveness** Time to eye opening: 10.9 thiopental and 7.0 propofol (p = 0.0025) Time to consciousness: 13.3 thiopental and 8.3 propofol (p = 0.0019) Time spent in recovery room: 142.6 thiopental and 111.46 propofol (p = 0.013) Time to orientation: 14.5 thiopental and 9.3 propofol (p = 0.0002) Time to tolerate fluid: 76.1 thiopental and 53.8 propofol (p = 0.06)
Jakobsson *et al*., 1997,[84] Sweden	Source: RCT Randomisation: NK Blind: NK Power estimate: NK Inclusion/ exclusion criteria: 5 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and drugs	Official list price	**Costs** Desflurane: SEK 40.5 ± 18 Propofol: SEK 114 ± 34 p < 0.01 **Effectiveness**[*] No differences

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	Economic checklist		
Kain *et al.*, 1994,[215] USA	Source: RCT Randomisation: NK Blind: single Power estimate: NK Inclusion/exclusion criteria: NK Recruitment rates: NK Representative sample: NK Comparable groups: NK	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics, time to recovery	Hospital accounts	**Costs** Propofol net saving: US $3228 **Effectiveness*** Propofol superior
Killian *et al.*, 1992,[86] Canada	Source: RCT Randomisation: yes Blind: no Power estimate: no Inclusion/exclusion criteria: 9 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and anti-emetics	Not known	**Costs** Propofol TIVA: total cost US $16.41 per patient Thiopental/isoflurane: total cost US $5.45 per patient **Effectiveness** No difference in terms of time to open eyes (immediate recovery), Aldrete score, time to orientation, PONV. Propofol TIVA was superior in terms of intermediate and late recovery, psychomotor tests and overall recovery
Kurpiers *et al.*, 1996,[216] USA	Source: RCT Randomisation: yes Blind: no Power estimate: no Inclusion/exclusion criteria: 8 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Drug	Hospital-specific prices	**Costs** Propofol TIVA: average cost US $31.77 ± 14.44; drug costs US $57.97 ± 20.22 Propofol/desflurane: average cost US $12.99 ± 7.61; drug costs US $34.86 ± 14.13 **Effectiveness** PONV: propofol 12% and desflurane 41% ($p < 0.05$)

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Meyer-McCright *et al*., 1998,[217] USA	Source: retrospective cohort Randomisation: no Blind: no Power estimate: no Inclusion/ exclusion criteria: 3 Recruitment rates: no Representative sample: no Comparable groups: no	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Total anaesthesia cost: anaesthesia time, staff, anaesthetics, drugs	Hospital-specific prices	**Costs** Thiopental/isoflurane: US $77.90 ± 23.30 Propofol/isoflurane: US $82.90 ± 18.80 Propofol/desflurane: US $87.10 ± 7.47 No difference in terms of discharge time **Effectiveness** NA
Nathan *et al*., 1998,[99] Canada	Source: RCT Randomisation: sealed envelope Blind: NK Power estimate: NK Inclusion/ exclusion criteria: 3 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and drugs to discharge	Not stated	**Costs** Sevoflurane: FF 679 Propofol: FF 1153 **Effectiveness*** Propofol may be superior in this patient group. Higher level of bleeding associated with sevoflurane
Patel *et al*., 1996,[218] USA	Cohort, unmatched controls	NA	Operation room exit times	Pharmacy	No differences in operating room exit times by anaesthetic agent

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	Economic checklist		
Ries *et al*., 1999,[219] Canada	Source: RCT Randomisation: CGRNT Blind: single Power estimate: NK Inclusion/exclusion criteria: 3 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and drugs	Hospital pharmacy	**Costs** Sevoflurane: CAN $38.10 ± 10.13 Isoflurane: CAN $23.87 ± 6.59 $p < 0.01$ **Effectiveness*** No differences
Rosenberg *et al*., 1994,[220] USA	Source: RCT Randomisation: NK Blind: single Power estimate: NK Inclusion/exclusion criteria: NK Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics	Not stated	**Costs** Propofol: US $44.08/h Desflurane: US $11.24/h **Effectiveness*** Not measured
Smith and Thwaites, 1999,[125] UK	Source: RCT Randomisation: sealed envelope Blind: double Power estimate: yes Inclusion/exclusion criteria: 3 Recruitment rates: NK Representative sample: NK Comparable groups: yes	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics	*British National Formulary*	**Costs** Sevoflurane: GBP 5.9 ± 1.5 Propofol: GBP 8.84 ± 4.49 **Effectiveness*** Propofol superior

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Smith *et al.*, 1999,[221] Belgium, France, The Netherlands, UK	Source: RCT Randomisation: yes, computer generated Blind: no Power estimate: no Inclusion/ exclusion criteria: 4 Recruitment rates: no Representative sample: no Comparable groups: no	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics, drugs and disposables	Country-specific prices converted to US $	**Costs** Propofol TIVA: US $31.9 Propofol/sevoflurane: US $19.7 Sevoflurane/sevoflurane: US $18.8 **Effectiveness** LMA insertion: TIVA 92.8, propofol/sevoflurane 87.2, sevoflurane/sevoflurane 140.3 ($p < 0.05$) Open eyes: TIVA 6.2, propofol/sevoflurane 7.2, sevoflurane/sevoflurane 6.0 ($p < 0.05$) Fit for discharge: TIVA 195.4, propofol/ sevoflurane 181.7, sevoflurane/sevoflurane 195.8 (NS) Nausea: TIVA 5.6%, propofol/sevoflurane 11.4%, sevoflurane/ sevoflurane 31.9% ($p < 0.05$) Vomiting: TIVA 0%, propofol/sevoflurane 8.6%, sevoflurane/sevoflurane 17.4% ($p < 0.05$)
Song *et al.*, 1998,[126] USA	Source: RCT Randomisation: CGRNT Blind: single Power estimate: yes Inclusion/ exclusion criteria: 7 Recruitment rates: NK Representative sample: NK Comparable groups: yes	NA	NA	NA	**Effectiveness** No differences between desflurane, sevoflurane and propofol in time to transfer to post-anaesthesia care unit

continued

***TABLE 71* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Sun *et al.*, 1999,[222] USA	Source: RCT Randomisation: CGRNT Blind: single Power estimate: NK Inclusion/ exclusion criteria: 7 Recruitment rates: NK Representative sample: NK Comparable groups: no	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetic and drug costs Nurse time PACU resources	Hospital accounts	**Costs** Methohexitone/desflurane: US $68.97 ± 20.74[a] Methohexitone/ sevoflurane: US $75.86 ± 27.63[a] Propofol/desflurane: US $89.78 ± 20.78 Propofol/sevoflurane: US $100.66 ± 36.6 [a] $p < 0.05$ vs propofol **Effectiveness**[*] No differences
Tang *et al.*, 1999,[129] USA	Source: RCT Randomisation: yes, computer generated Blind: single Power estimate: yes, based on 80% power and 25% reduction in mean total cost Inclusion/ exclusion criteria: 3 Recruitment rates: – Representative sample: – Comparable groups: –	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics, analgesics and anti-emetics Nursing staff	Hospital-specific prices	**Costs** (incremental) Drugs: propofol TIVA, US $24.8; propofol/ sevoflurane, US $25.7; sevoflurane/sevoflurane, US $19.64 Recovery costs: propofol TIVA, US $21.49; propofol/sevoflurane, US $29.73; sevoflurane/ sevoflurane, US $30.76 Perioperative costs: propofol TIVA, US $46.3; propofol/sevoflurane, US $55.41; sevoflurane/ sevoflurane, US $50.10 **Effectiveness** Patient satisfaction: propofol TIVA, 100%; propofol/sevoflurane, 88%; sevoflurane/sevoflurane, 70% Recovery nausea: propofol TIVA, 3; propofol/ sevoflurane, 18; sevoflurane/sevoflurane, 40 ($p < 0.05$) Vomiting: propofol TIVA, 0; propofol/sevoflurane, 15; sevoflurane/sevoflurane, 17. ($p < 0.05$) Cost to achieve complete satisfaction in one patient: propofol TIVA, US $46.3, propofol/sevoflurane, $62.97; sevoflurane/ sevoflurane, $71.57

continued

***TABLE 11* contd** *Quality of cost or economic comparisons of anaesthetic agents*

Study	Study design	Resources measured and costed		Source of costs	Results
		Data collection	**Economic checklist**		
Wagner *et al*., 1995, USA	Source: RCT Randomisation: NK Blind: open Power estimate: insufficient Inclusion/ exclusion criteria: NK Recruitment rates: NK Representative sample: NK Comparable groups: NK	Study design: INAD Effectiveness data: INAD Outcome data: NA Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics and drugs, operating theatre, recovery room	Hospital charges	**Costs** Isoflurane US $2230 ± 198 Sevoflurane US $2641 ± 174 **Effectiveness*** No differences
Wagner and O'Hara, 1997,[223] USA	Source: retrospective cohort Randomisation: no Blind: no Power estimate: no Inclusion/ exclusion criteria: 4 Recruitment rates: – Representative sample: – Comparable groups: –	Study design: INAD Effectiveness data: INAD Outcome data: INAD Cost data: UNACC Analysis: INAD Sensitivity analysis: no	Anaesthetics, theatre room, recovery room	Hospital-specific charges	**Costs** Total drug costs: propofol, US $26.80 ± 9.89; thiopental, US $20.85 ± 8.26 ($p$ = 0.0001) Total non-drug costs: propofol, US $3126.00 ± 1047.00; thiopental, US $3404.00 ± 1021.00 ($p$ = 0.0387) Total: propofol, US $3152.00 ± 1053.00; thiopental, US $3425.00 ± 1028.00 ($p$ = 0.0443) **Effectiveness** NA

Data collection: CGRNT, computer-generated random numbers table

Study design: good = criteria 1–7, 20 and 21 met; AD = criteria 1, 3, 5, 6 and 20 met; INAD = one or more of criteria 1, 3, 5, 6 and 20 not met

Effectiveness data: good = criteria 8–11 met; AD = criteria 8 and 11 met; INAD = one or more of criteria 8 and 11 not met

Outcome data: good = criteria 12–15 met; AD = criteria 12 and 14 met; INAD = one or more of criteria 12 and 14 not met

Cost data: ACCEPT = criteria 16–19 met; UNACC = one or more of criteria 16–19 not met

Analysis: good = criteria 22–35 met; AD = criteria 22, 23, 26, 27, 29, 30, 31 met; INAD = one or more of criteria 22, 23, 26, 27, 29, 30 and 31 not met

NA, not appropriate/relevant; NK, not known or not reported

* *Defined by author*

Appendix 10

Studies excluded from the literature review

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Appendix 11

National survey of anaesthetic practice

STUDY OF ANAESTHETIC AGENTS & TECHNIQUES IN DAY CASE SURGERY

(CESA)

National survey of anaesthetic practice in day case surgery

October 2000

We are interested in the anaesthetic agents and techniques you use for specific types of day case surgery. Please answer the questions that are relevant to your practice as an anaesthetist by placing a tick in the relevant box ☐ or writing in the space _____ provided, unless otherwise instructed. Please tick just one box for each type of day case surgery. We are interested in your routine practice. Where appropriate, please circle the route of administration and specify the dose (mg/kg) or flow rate (%). Thank you.

PREMEDICATION

1. What premedication do you **routinely** use for day case surgical patients in adult urology, adult orthopaedics and paediatrics (3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] not given	☐	☐	☐
[b] benzodiazepine	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.
[c] If benzodiazepine or other please specify type & route	type: _____ oral/i.v./i.m./s.c./p.r.	type: _____ oral/i.v./i.m./s.c./p.r.	type: _____ oral/i.v./i.m./s.c./p.r.

2. In what percentage of ***your*** day case patients do you **routinely** use premedication?
Please try and estimate the approximate figure. We do not require the exact percentage.

adult urology _____% e.g. cystoscopy | adult orthopaedic _____% e.g. knee arthroscopy | paediatric (3–12 years) _____% e.g. circumcision

INDUCTION

3. What induction agent do you **routinely** use for day case surgical patients in adult urology, adult orthopaedics and paediatrics(3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] etomidate	☐ dose: _____	☐ dose: _____	☐ dose: _____
[b] halothane	☐ %: _____	☐ %: _____	☐ %: _____
[c] midazolam	☐ dose: _____	☐ dose: _____	☐ dose: _____
[d] propofol	☐ dose: _____	☐ dose: _____	☐ dose: _____
[e] sevoflurane	☐ %: _____	☐ %: _____	☐ %: _____

[f] thiopentone	☐ dose:	☐ dose:	☐ dose:
[g] other *please specify type, dose & route*	☐ type & dose:	☐ type & dose:	☐ type & dose:
	i.v./inhalation	i.v./inhalation	i.v./inhalation

MAINTENANCE

4. What maintenance agent do you **routinely** use for day case surgical patients in adult urology, adult orthopaedics and paediatrics (3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] enflurane	☐ %:	☐ %:	☐ %:
[b] halothane	☐ %:	☐ %:	☐ %:
[c] isoflurane	☐ %:	☐ %:	☐ %:
[d] propofol	☐ dose:	☐ dose:	☐ dose:
[e] sevoflurane	☐ %:	☐ %:	☐ %:
[f] other *please specify type, dose & route*	☐ type & %/dose:	☐ type & %/dose:	☐ type & %/dose:
	inhalation/i.v.	inhalation/i.v.	inhalation/i.v.

INTRAOPERATIVE PERIOD

5. What prophylactic anti-emetic do you **routinely** use for day case surgical patients in adult urology, adult orthopaedics and paediatrics (3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] not given	☐	☐	☐
[b] cyclizine	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[c] droperidol	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[d] metoclopramide	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[e] ondansetron	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.

[f] prochlorperazine	☐ oral/i.m./p.r.	☐ oral/i.m./p.r.	☐ oral/i.m./p.r.
[g] other *Please specify Type and route*	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.

6. In what percentage of ***your*** day case patients do you routinely use prophylactic anti-emetics?
Please try and estimate the approximate figure. We do not require the exact percentage.

adult urology _____% adult orthopaedic_____% paediatric (3–12 years) _____%

7. What local anaesthetic do you favour to **routinely** use as an adjunct to general anaesthesia for day case surgical patients in adult urology, adult orthopaedics and paediatrics (3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] not given	☐	☐	☐
[b] bupivacaine	☐ 0.25%/0.375%/0.5%	☐ 0.25%/0.375%/0.5%	☐ 0.25%/0.375%/0.5%
[c] lignocaine	☐ 0.5%/1.0%/2.0%	☐ 0.5%/1.0%/2.0%	☐ 0.5%/1.0%/2.0%
[d] bupivacaine & adrenaline 1 in 200 000	☐ 0.25%/0.375%/0.5%	☐ 0.25%/0.375%/0.5%	☐ 0.25%/0.375%/0.5%
[e] lignocaine & adrenaline 1 in 200 000	☐ 0.5%/1.0%/2.0%	☐ 0.5%/1.0%/2.0%	☐ 0.5%/1.0%/2.0%
[f] other *please specify type and concentration*	☐ type and concentration: _____	☐ type and concentration: _____	☐ type and concentration: _____

8. What intraoperative analgesic(s) do you **routinely** use for day case surgical patients in adult urology, adult orthopaedics and paediatrics (3–12 years)?

	ADULT UROLOGY **e.g. cystoscopy**	ADULT ORTHOPAEDIC **e.g. knee arthroscopy**	PAEDIATRIC **e.g. circumcision**
[a] not given	☐	☐	☐
[b] alfentanil	☐	☐	☐
[c] diamorphine	☐ i.v./i.m./s.c./p.r.	☐ i.v./i.m./s.c./p.r.	☐ i.v./i.m./s.c./p.r.
[d] diclofenac	☐ i.v./i.m./p.r.	☐ i.v./i.m./p.r.	☐ i.v./i.m./p.r.
[e] fentanyl	☐	☐	☐

[f] ketorolac	☐ i.v./i.m.	☐ i.v./i.m.	☐ i.v./i.m.
[g] morphine	☐ i.v./i.m./s.c.	☐ i.v./i.m./s.c.	☐ i.v./i.m./s.c.
[h] pethidine	☐ i.v./i.m./s.c.	☐ i.v./i.m./s.c.	☐ i.v./i.m./s.c.
[i] remifentanil	☐	☐	☐
[j] other *please specify type and route*	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.

In questions 9 to14 please try and estimate the approximate figure. We do not require the exact percentage.

9. In what percentage of ***your*** day case patients do you routinely use a **local anaesthetic** as an adjunct to general anaesthesia?

adult urology _____% adult orthopaedic_____% paediatric (3–12 years) _____%

10. In what percentage of ***your*** day case patients do you routinely use a **neuromuscular blocking agent**?

adult urology _____% adult orthopaedic_____% paediatric (3–12 years) _____%

11. In what percentage of ***your*** day case patients do you routinely use **suxamethonium**?

adult urology _____% adult orthopaedic_____% paediatric (3–12 years) _____%

12. In what percentage of ***your*** day case patients do you routinely use a **laryngeal mask airway (LMA)**?

adult urology _____% adult orthopaedic_____% paediatric (3–12 years) _____%

13. What **oxygen** flow rate (l/min) do you routinely use in ***your*** day case patients?

[a] *Induction*
adult urology _____l/min adult orthopaedic_____ l/min paediatric (3–12 years) _____l/min

[b] *Maintenance*
adult urology _____l/min adult orthopaedic_____l/min paediatric (3–12 years)_____l/min

14. What **nitrous oxide** flow rate (l/min) do you routinely use in ***your*** day case patients?

[a] *Induction*
adult urology _____l/min adult orthopaedic_____l/min. paediatric (3–12 years)_____l/min

[b] *Maintenance*
adult urology _____l/min adult orthopaedic_____l/min paediatric (3–12 years)_____l/min

POSTOPERATIVE NAUSEA AND VOMITING (PONV)

15. What anti-emetics do you **routinely** use for the **treatment** of PONV for day case surgical patients in adult urology, adult orthopaedic and paediatrics (3–12 years)? ***Please indicate your 1st & 2nd line drug by writing 1 & 2 in the relevant box*** ☐ ***. Select just two agents for each type of day case surgery.***

	ADULT UROLOGY e.g. cystoscopy	ADULT ORTHOPAEDIC e.g. knee arthroscopy	PAEDIATRIC e.g. circumcision
[a] cyclizine	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[b] droperidol	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[c] metoclopramide	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.	☐ oral/i.v./i.m.
[d] ondansetron	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.	☐ oral/i.v./i.m./p.r.
[e] prochlorperazine	☐ oral/i.m./p.r./buccal	☐ oral/i.m./p.r./ buccal	☐ oral/i.m./p.r./ buccal
[f] other *please specify type and route*	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.	☐ type: _____ oral/i.v./i.m./s.c./p.r.

ABOUT YOUR NHS TRUST AND DAY CASE SURGERY

16. What is your grade ? Consultant ☐ SpR ☐ Senior registrar ☐
Associate specialist ☐ Staff grade ☐
Senior house officer ☐ Other ☐
If other, please specify_____

17. Does your NHS Trust have a dedicated day case ward or unit? yes ☐ no ☐

In questions 18 & 19 please try and estimate the approximate figure. We do not require the exact percentage or number of minutes.

18. What percentage of ***your*** day case patients are:
adult urology _____% adult orthopaedic_____% paediatric (3–12 years)_____%?

19. What is the average length of time for a day case operation in:
adult urology _____min adult orthopaedic_____min paediatric (3–12 years)_____min?

COMMENTS

If you have any further comments or suggestions then please use this space here to write them.

Please tick ☐ *If you would be interested in a summary of the results of this survey.*

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE. NOW PLEASE RETURN IT TO US USING THE FREEPOST ENVELOPE

Appendix 12

The scientific advisory group

Membership

Dr John Sear (Chair), Reader in Anaesthesia and Honorary Consultant Anaesthetist, Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford, UK.

Professor Francis Creed, Professor of Psychological Medicine, School of Psychiatry and Behavioural Sciences, Manchester Royal Infirmary and Research Dean, Medical School, University of Manchester, UK.

Dr Chris Roberts, Senior Lecturer in Biostatistics, School of Epidemiology & Health Sciences, University of Manchester, UK.

Dr Stirling Bryan, Senior Lecturer in Health Economics, Health Services Management Centre, University of Birmingham, UK.

Contribution

The scientific advisory group (SAG) was set up to advise the project team, meeting every 3–6 months. The group commented on all key aspects of project design and execution, advising on problems or conflicts of a technical or scientific nature.

The main work of the SAG included assistance with:

- adherence to protocol and commissioning brief; and approval of protocol changes
- compliance with the CONSORT (Consolidated Standards for Reporting Trials) guidelines
- assistance with decisions relating to recruitment and sample size
- setting early termination criteria
- overseeing quality control procedures and monitoring processes
- reviewing project documents and instruments (practice survey, interview schedules, data collection procedures, quality assurance procedures, interim analysis/report, final analysis/report)
- monitoring progress against agreed milestones
- assistance with publication strategy.

Appendix 13

Development of the contingent valuation tool

The aim of this study was to develop and test a CV tool to identify and quantify women's preferences for alternative anaesthetic agents in day surgery. The objectives were:

- to develop and test hypothetical scenarios, which describe the expected outcomes of the alternative anaesthetic agents being compared
- to identify and quantify women's preferences for alternative anaesthetic agents for induction and maintenance of anaesthesia
- to assess the respondents' ability to carry out the valuation using the hypothetical scenarios developed.

Methods

CVs were required to assess incremental willingness to pay for either inhalational or intravenous induction (scenario 1) or maintenance (scenario 2). Hypothetical scenarios for each of these cases were required. In-depth interviews with two female university administrative staff who had undergone gynaecological day surgery were used to develop the topic guide and appropriate language for the semi-structured interviews and the CV scenarios.

Instrument development

CV constitutes a group of methods that elicit valuations from respondents, each with their own strengths and weaknesses.[231,232] There is no standard approach to the development of a CV tool.[232] However, increasing amounts of empirical evidence provide some guidance on design.

This study examined the willingness to pay for one alternative over another. This equates to the maximum amount of money that must be taken from an individual to equalise a utility change.[231] We aimed to elicit incremental, rather than absolute, willingness-to-pay values for one alternative over another. Patients would only ever have to choose between types of anaesthetics, so a 'no treatment' scenario was not included.

Elicitation of willingness-to-pay values is most commonly carried out using direct (open ended) questions. However, such questions may produce contradictory answers, protest answers or no answers at all.[231] The most suitable choice of the better close-ended methods (which constrain the valuations given by respondents) remains unresolved. Of the available options, we chose payment cards. Respondents indicated a monetary figure on a VAS that reflected how much they valued their preferred anaesthetic. To minimise range bias, respondents were told that they could also give valuations beyond the VAS.

Previous experience of surgery, day surgery and anaesthesia was therefore investigated for their impact on willingness-to-pay values. The payment vehicle used was private money and income was measured as bands of household income.

Two hypothetical scenarios were developed (see appendices 14 and 15). Scenario 1 determined women's preferences for induction agents. Respondents were asked to compare propofol (referred to as medicine A) and sevoflurane (medicine B). Scenario 2 determined women's preferences for maintenance agents. Respondents were asked to compare isoflurane (medicine C) and propofol (medicine D). The side-effect profiles used reflect those experienced after gynaecological day-surgery anaesthesia.[45]

Study sample and recruitment

The study took the perspective of female members of the public who may, or may not, have had previous experience of an operation or day surgery. The study recruited female members of administrative and secretarial staff, based in the engineering, physics and accounting departments at the university. This was to obtain a sample with a range of ages and educational backgrounds. Non-medical and non-clinical departments were deliberately selected to ensure that prior medical knowledge more closely matched that of the general population. Women were identified from the telephone directory and invited to participate by letter. It was not possible to carry out a prior power analysis to determine sample size. Forty to fifty interviews were deemed necessary to identify variations in understanding, perception and ability to carry out the CV.

Interviews

A pilot study with five women was carried out and minor modifications were made to the interview schedule and survey instruments. The same researcher conducted semi-structured, face-to-face, interviews, with 40 women. All interviews were tape-recorded, with permission.

Results

Fifty-four women were invited to take part and 40 (74%) were recruited to the study. Fourteen women refused to take part in the study, due to lack of time ($n = 6$) or interest ($n = 8$). The mean age of the sample was 40 years (range 20–60 years). Ten (25%) respondents had a total monthly household income between £500 and £1000, 17 (43%) respondents were in the income band £1001 to £2000, and 11 (28%) respondents had a monthly household income of more than £2000.

Stated preference for anaesthetic agents

Induction

Of the 36 respondents who had previously undergone operation, 29 (73%) stated that they would prefer propofol and 7 (17%) that they would prefer sevoflurane. All four respondents (100%) who had no previous experience of operations stated that they would prefer sevoflurane. This association between respondents' preferences and their experience of operations was statistically significant ($\chi^2 = 6.89$, degrees of freedom (df) = 1; $p < 0.01$).

Most women preferred propofol if they had past experience of receiving an anaesthetic via a mask. Twenty-five (63%) respondents had a previous experience of a mask and 23 (92%) of these stated that they would prefer propofol ($\chi^2 = 15.00$, df = 1; $p < 0.001$). Twenty-nine (73%) respondents had experience of injections, but this did not affect the stated preferences.

Respondents were asked to explain why they preferred their chosen anaesthetic agent. Respondents preferred to receive propofol, because either they had a previous unpleasant experience of receiving an anaesthetic via a mask or they had a previous unproblematic experience of injections. All four respondents (10%) with no experience of operations preferred to receive sevoflurane. Respondents' reasons included an inherent fear of pain or injections, combined with the fact that gas was described as tasteless.

Scenario 2

As expected, all respondents preferred to receive propofol, the option with the lowest risk of PONV.

Monetary valuation of preferences

Thirty-eight (95%) respondents attached an incremental willingness-to-pay value to their preference in scenario 1. Of the 29 (73%) respondents who preferred propofol, 24 (83%) attached a value to their preferences, 3 (10%) attached zero and 2 (7%) did not attach a value (*Table 72*). All 11 (30%) respondents who preferred sevoflurane attached a value to their preference.

Of the maintenance anaesthetics, all 40 respondents preferred propofol. Thirty-four (85%) attached a value to their preferences, 4 (10%) attached a zero value and 2 (5%) did not attach a value. The mean willingness-to-pay value was £156.50 (median £150.00, range £0.00–750.00), excluding respondents who did not attach a value.

Assessment of respondents' understanding

Open questions revealed that 34 (85%) respondents understood the CV tool. Six respondents (15%) did not appear to understand what they were being asked to value, or believed they were assessing the cost of the anaesthetics. Removal of the CVs of these six respondents did not significantly change the overall values in this study.

Discussion

This study developed and tested a CV tool to determine women's preferences for alternative

TABLE 72 *Incremental willingness to pay values for scenario 1*

Preferred induction agent	CV (£)			No. of respondents
	Mean	Median	Range	
Propofol (medicine A)	208.30	150.00	0.00–1000.00	27
Sevoflurane (medicine B)	104.50	100.00	0.00–200.00	11

anaesthetics in day surgery, using a sample of female members of the public.

We proposed that, if the approach were valid, the women would be able to explain the reason for how much they were willing to pay to receive one medicine and avoid receiving the other. Most respondents understood what they were being asked to value and placed a valuation on how much they wanted to receive their preferred agent.

This study was performed for methodological development and testing, so the sample did not need to be representative of the population. The results of this study were not generalisable to the UK population. All study respondents were female members of the public, which may have influenced the willingness-to-pay values obtained in this study. However, it is suggested that the instrument may be suitable for different patient groups in day surgery and, with modification, in inpatient surgery.

Women can be divided into those with currently no experience (*ex ante*) and those with experience of the procedure (*ex post*). These results highlight the need for studies looking at patient preferences to be explicitly *ex post* or *ex ante*, to avoid implicit information bias.[233] Reviews of empirical CV have similarly concluded that experience of the treatment affects willingness-to-pay values.[23,34,234] Cost–benefit analysis should only include *ex post* valuations in the same proportions as occur in the population, to avoid biasing overall valuation averages.[232]

Current empirical evidence and reviews suggest that the ideal design for a CV study remains unresolved. This lack of consensus is illustrated in the debate on elicitation methods. The dichotomous choice method, or 'take it or leave it', has been recommended by the US National Oceanic and Atmospheric Administration.[235] Respondents are asked whether they are willing to pay a single amount, which is varied through the necessarily large sample. Although this is supposed to be closest to real market decisions, it may be open to 'yea-saying' bias.[231] The use of 'bidding' can lead to starting point bias, and the use of 'payment cards' (as in this study) can lead to range bias,[232] despite higher response and completion rates. The impact of range bias has been investigated, and one study reported that, by doubling the range, the willingness-to-pay values increased by 30%.[236] However, another study found that range changes did not produce significantly different willingness-to-pay values.[237]

Similarly, there is no consensus regarding payment vehicles, which is a particular concern in publicly funded health systems, where this may lead to strategic bias.[231,234] This is a risk in the UK, where respondents may give very high or very low values to have an effect on service implementation. It is also suggested that respondents have an incentive to state high values for their preferred alternative, as they do not expect any individual charges. However, the evidence to support this proposed bias is lacking. Although healthcare is generally publicly funded in the UK, there is increasing contribution from the individual. Therefore, it does not necessarily follow that the payment vehicle used in UK CV studies must be taxation. Due to the transient and relatively mild nature of the adverse drug reactions under investigation here, taxation or insurance premiums were not considered appropriate payment vehicles. Indeed, it may be argued that management of PONV is within the realms of self-management, so private money is a more appropriate payment vehicle.

Methodological debate aside, the primary concern, for both advocates and critics of the CV, is the hypothetical nature of the scenarios, the contingent market, and thus the valuations elicited. As stated by Carson and Mitchell[238] "only questions that create a realistic market for a precisely defined good can measure the type of income-constrained behavioural intention information suitable for use in an economic evaluation". To this end, great efforts were made in this study to develop realistic scenarios with understandable language and minimum bias. However, there is concern that respondents have difficulty responding because of the hypothetical nature of the questions. Although this study found a small minority of respondents with this problem, other studies have reported a far greater proportion of respondents unable to carry out the task. In a study assessing community values in healthcare, two-thirds of respondents had problems.[239] There is no evidence that hypothetical bias exists in one direction or another.[231] However, assessing the extent of potential hypothetical bias is an important research agenda for the future. Uncertainty about the validity of this hypothetical market arises from its contingent nature causing artificiality. There are concerns that the values are constructed in response to the questions and that they do not exist before they are measured.[240] Furthermore, it is not clear whether expressed values bear any relation to actual values or predict future behaviour. At this time, there is no healthcare study that has compared

hypothetical CV responses with actual market rates, so the debate must remain unresolved.

In conclusion, this study developed a CV instrument to address an increasingly common issue in healthcare: Are seemingly minor improvements in the process of healthcare important to patients? Conceptual and measurement issues in the measurement of patient preferences in general, and in CV in particular, remain to be addressed. In its favour is the large body of empirical evidence and high levels of scrutiny shown in developing and testing the method. The patient, or consumer of healthcare, is having increasing influence on health policy, and rightly so. Therefore, it is essential that valid methods for eliciting their preferences are developed and applied.

The CV instrument developed in this study was used in the empirical study.

Appendix 14

Contingent valuation scenario for induction of anaesthesia

The medicines used to put you to sleep

'Imagine that you have an operation under a general anaesthetic [medicine which makes you go to sleep]. You will receive the general anaesthetic immediately before undergoing the operation, either by an injection into your hand or arm, or a facemask. You will wake up quickly after the operation. The whole procedure will take between 30 and 60 minutes. You will be discharged from hospital on the same day after about 5 hours. Examples of operations might be cataract removal, having wisdom teeth out or a varicose vein removal.'

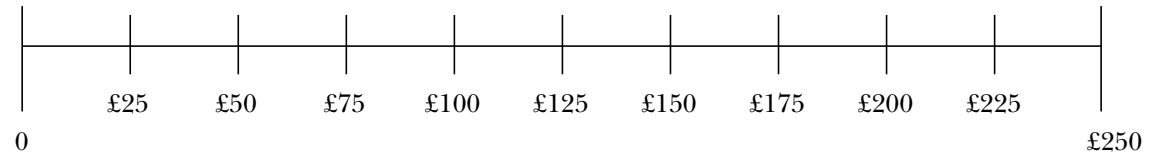
'Medicine A'

Will be given to you by an injection in a vein in your hand or arm. This may cause pain at the site of injection for 1 out of 4 patients. This pain may be severe, which means a lot more than normal pain you would expect at the injection site, for 1 out of 40 patients.

'Medicine B'

Will be given to you by means of breathing it in using a facemask and it is tasteless with a sweet smell.

Scale



..... Or more than £250

Reproduced from Elliott and co-workers,[33] by permission of Swedish Pharmacuetical Press.

Appendix 15

Contingent valuation scenario for maintenance of anaesthesia

The medicines used to keep you asleep

'Imagine that when you have the operation you have been given a medicine to put you to sleep. Then you need to be kept asleep during the operation. There are two different medicines that could be used for this. Like all medicine used to keep you asleep during an operation they may both have some side-effects such as sickness [you may feel sick or actually be sick].'

'Medicine C'

May cause sickness, either feeling sick or being sick. This seems to happen in about 7 out of 10 patients. People are rarely actually sick after the first day, but some people may feel sick for up to 2 days and sometimes for up to 4 days after the operation.

'Medicine D'

May cause sickness, either feeling sick or being sick. This seems to happen in about 3 out of 10 patients. People are rarely actually sick after the first day, but some people may feel sick for up to 2 days and sometimes for up to 4 days after the operation.

Scale

..... Or more than £250

Reproduced from Elliott and co-workers,[33] by permission of Swedish Pharmacuetical Press.

Appendix 16

Patients' views, experiences and preferences for day-case anaesthesia

Background

The empirical study quantified the relative costs, patient benefits and acceptability of alternative anaesthetic agents and related techniques. The main focus of the study was to explore the patients' perspective of anaesthetics for day surgery. For this reason a study was designed to explore the views, experiences and preferences of patients undergoing day surgery.

Method

The views and experiences of patients undergoing day surgery were explored during telephone interviews conducted around day 7 postdischarge.

Parents or guardians of children undergoing day surgery were asked the following questions in the structured telephone interview:

- Did your son/daughter experience any discomfort from the injection or mask used to send them sleep?
- Has your son/daughter had an operation before this one and if so what?
- What similarities or differences did you notice between the anaesthetic your son/daughter received in this study and ones they have had in the past?
- Did you feel ready to take your son/daughter home from hospital when you did?
- Were you satisfied with the care your son/daughter received (a) on the ward before the operation, (b) in the recovery area immediately after the operation, (c) on the ward after the operation?

The following open questions were asked in the structured telephone interview with adult patients:

- Did you have an injection or a mask to send you to sleep for your operation?
- Did you experience any discomfort from the injection or mask used to send you to sleep?
- Have you had an operation before this one and if so what?
- What similarities or differences did you notice between the anaesthetic you received in this study and ones you have had in the past?
- Did you feel ready to go home from hospital when you did?
- Were you satisfied with the care you received (a) on the ward before the operation, (b) in the recovery area immediately after the operation, (c) on the ward after the operation?

These telephone interviews were also used to explore the direction and strength of preference (willingness to pay) for induction and maintenance anaesthetics (see chapter 4). Descriptive scenarios of the process and outcome of anaesthesia were developed for both adult and paediatric patient groups (see chapter 4). Respondents were provided with two scenarios:

- Scenario 1: valuation of intravenous (medicine A) versus inhalational (medicine B) induction (see appendix 14).
- Scenario 2: valuation of intravenous (medicine D) versus inhalational (medicine C) maintenance (see appendix 15).

Two questions were asked to explore the understanding of the exercise, and thus the validity of the valuation given. First, respondents were asked why they selected their preferred anaesthetic for each scenario. Second, respondents were asked about the reasoning behind their stated willingness-to-pay value for each scenario.
All responses to these questions were recorded verbatim as closely as possible, but in some instances respondents' answers were paraphrased.

A thematic framework approach was used to analyse the responses to the open questions.[241] The responses were read thoroughly to identify the emerging themes. A theme was identified by grouping together statements with a common property. The main themes that emerged were listed under headings. Individual statements were then re-read and coded according to the theme headings identified. The codes were used to group the themes and quantify the number of times each

theme occurred. Some respondents mentioned more than one theme in their answer.

One researcher coded the statements. The coding of the statements was checked for consistency by a second researcher (intercoder reliability) in a subsample of the statements.[242] A meeting was then held to discuss the consistency of the coding, and consensus was reached.

Results and discussion

Parents' or guardians' views

A total of 260 (81%) parents or guardians whose son/daughter was enrolled in the empirical study were telephoned. Of these, 51% (n = 132) of the children had received propofol induction and halothane maintenance anaesthesia (propofol/halothane) and 49% (n = 128) of the children had received sevoflurane induction and maintenance anaesthesia (sevoflurane/sevoflurane).

Discomfort from injection or mask

Around one-third of parents or guardians felt their child experienced some discomfort from the injection used to give propofol (37%) or the mask used to give sevoflurane (31%). For the injection this discomfort may have been due to the cannula being put in place as this parent described:

> "He said it was hurting when putting the needle in. Afterwards it was sore, it was bruised" [pgnma196].

or it may have been due to the propofol itself:

> "Yes, he had a lot of pain or burning sensation in his arm" [penma078].

For the mask, the discomfort described was due to the taste or smell of the gas, as this parent described:

> "After the operation he said he could taste the gas and it wasn't nice" [penma060].

or because their child seemed frightened by the experience of having the mask:

> "I was put off a little by the mask over her face" [penfa026].

Anaesthetic comparisons

The parents or guardians reported that less than half (47% for propofol/halothane and 44% for sevoflurane/sevoflurane) of the children had experienced an operation before this one. Previous operations were mainly for day procedures, such as adenoidectomy, circumcision, insertion of grommets or tonsillectomy.

Table 73 summarises the parents' or guardians' comparisons made between the anaesthetic their son/daughter had this time and previous anaesthetics experienced.

TABLE 73 *Comparisons with previous anaesthetics in the paediatric study*

Comparison	No. of parents/guardians	
	Propofol/ halothane (n = 132)	Sevoflurane/ sevoflurane (n = 128)
Can't remember	5 (4%)	4 (3%)
No difference	20 (15%)	7 (5%)
Less drowsy with this one	15 (11%)	9 (7%)
More drowsy with this one	5 (4%)	4 (3%)
Less calm with this one	9 (7%)	8 (6%)
More calm with this one	8 (6%)	13 (10%)
Less sick with this one	0 (0%)	2 (2%)
More sick with this one	0 (0%)	4 (3%)
Did not like the injection/ mask	2 (2%)	1 (1%)

Ready to leave hospital

The majority (98% for the propofol/halothane group and 99% for the sevoflurane/sevoflurane group) of parents or guardians felt ready to take their son/daughter home when they did, as this one explained:

> "Yes – felt they were not chasing us out" [pgnma197].

The minority who were not satisfied felt their son/daughter should have stayed longer because their son/daughter was sick, either in the car, or at home:

> "I wasn't sure, maybe he should have stayed longer, he was sick on the way home, we had to stop the car" [pgnma080].

All these children (3%) had received sevoflurane for induction and maintenance.

Some parents or guardians felt they wanted their son/daughter to sleep longer before they were discharged:

> "... would have felt happier if he could have slept longer before discharge" [penma081].

Satisfaction with care

Nearly all (99%) of the parents and guardians were very satisfied with the care their son/daughter received during the day-case episode. The satisfaction with care was not dependent on the type of anaesthetic received. Those parents or guardians who were not happy referred to a specific request that they had concerns about:

> "... would have preferred her to have a sedative and go to theatre on a trolley" [penfa025].

or had concerns about the success of the surgery:

> "... not completely satisfied, he seems to have repeated ear infections" [penma024].

> "Nursing staff were great but I had to wait to see the consultant. I didn't like to be spoken to in public and didn't get a reasonable explanation from the consultant about further surgery my son requires" [penma016].

Days to recover after the operation

The parents or guardians were asked to recall how many days it took their son/daughter to recover from the operation and resume their normal activities. There was no difference between the propofol/halothane and sevoflurane/sevoflurane groups. On average, the parent or guardian felt it took 3 days (95% CI, 2.3 to 3.8 for propofol/halothane; 95% CI, 2.2 to 3.9 for sevoflurane/sevoflurane) for their son/daughter to recover from their operation.

Parents' or guardians' preferences for induction

Table 74 summarises the reasons why parents or guardians would choose the injection (medicine A) or the mask (medicine B) to send their son/daughter to sleep for a future day procedure (see chapter 4 for the overall number who preferred medicine A or B).

Most parents or guardians who chose the injection did so because they felt the mask would be a frightening experience for their son/daughter, as this parent explained:

> "I do not like the idea of a mask being held over his face" [penma140].

Some parents or guardians based their preference on what happened when their son/daughter took part in the empirical study:

> "He was a bit worried about it and didn't like the mask. He can be distracted from the injection" [penma214].

TABLE 74 *Reason given for preference for induction method in the paediatric study*

Reason given	No. of parents/guardians	
	Propofol/halothane (*n* = 132)	Sevoflurane/sevoflurane (*n* = 128)
Preference for medicine A (injection)		
Mask is distressing/frightening	40 (30%)	5 (4%)
The injection works quicker	14 (11%)	7 (5%)
Son/daughter did not experience any pain	8 (6%)	1 (0.5%)
The injection is fine	8 (6%)	1 (0.5%)
Son/daughter wants the injection because had it before	3 (2%)	3 (2%)
Less drowsy with the injection	3 (2%)	0 (0%)
No experience of the mask	3 (2%)	0 (0%)
The gas makes my son/daughter sick	3 (2%)	0 (0%)
Son/daughter does not like the smell/taste of the gas	0 (0%)	3 (2%)
Preference for medicine B (mask)		
Injection is painful	29 (22%)	49 (38%)
Injection is distressing/frightening	4 (3%)	28 (22%)
Son/daughter wants the mask because had it before	3 (2%)	8 (6%)
The mask smells sweet	1 (0.5%)	5 (4%)
The mask 'sounds' better	4 (3%)	1 (0.5%)
Less drowsy with the mask	0 (0%)	3 (2%)
The mask works quicker	0 (0%)	1 (0.5%)

The majority of parents or guardians who chose the mask did so because of the chance their son/daughter might experience pain with the injection, as described by this parent:

> "... because of the pain and distress he has with injections" [pgnma106].

Parents' or guardians' strength of preference for induction of anaesthesia with an injection or a mask was quantified using willingness to pay (see chapter 4). The respondents were asked to explain why they stated the value they did, and the majority seemed to understand the concept of willingness to pay. However, some respondents (9 propofol/halothane; 12 sevoflurane/sevoflurane) did not understand the question and used the values on the scale like a VAS:

> "... because it is in the middle" [pgnma200, willingness to pay £125].

Two parents gave protest values and said:

> "... because you shouldn't have to pay" [penma040, willingness to pay £0].

These values (8% propofol/halothane, 10% sevoflurane/sevoflurane) were excluded from the main analysis of the willingness-to-pay values (see chapter 5).

Table 75 summarises the reasons behind the parents' or guardians' willingness-to-pay values for the preferred induction agent.

The majority of parents or guardians stated a value that expressed how much they would pay to accept the injection or mask:

> "... because she was so well with the injection" [penfa012, willingness to pay £250]
>
> "I thought it [the mask] was very good for him" [pgnma028, willingness to pay £250].

Some parents or guardians stated a value that reflected how much they would pay to avoid having the injection or mask:

> "I don't want her stressed and frightened by having the injection" [penfa074, willingness to pay £250]
>
> "The mask is frightening, I really do not want her to have it" [penfa089, willingness to pay £250].

Parents' or guardians' preferences for maintenance

Table 76 summarises the reasons behind the parents' or guardians' stated preference for medicine D compared to medicine C for the maintenance of anaesthesia. The parents or guardians were expected to choose medicine D because it had a lower incidence of nausea or vomiting compared to medicine C. Three respondents stated a preference for medicine C and one did not state a preference because they did not understand the question. The associated willingness-to-pay values were excluded from the analysis in the empirical study.

Parents' or guardians' strength of preference for maintenance of anaesthesia with a lower chance of

TABLE 75 *Reason given for willingness to pay for induction method in the paediatric study*

Reason given	No. of parents/guardians	
	Propofol/halothane (*n* = 132)	Sevoflurane/sevoflurane (*n* = 128)
Willingness to pay for medicine A (injection)		
Injection seems better (willingness to accept)	36 (27%)	5 (4%)
Mask is distressing/frightening (willingness to avoid)	22 (17%)	11 (9%)
Would have the mask if advised or had to	13 (10%)	4 (3%)
Like to have the choice	3 (2%)	2 (2%)
No experience of the mask	5 (4%)	0 (0%)
Did experience some pain, but still prefer it	1 (0.5%)	0 (0%)
Willingness to pay for medicine B (mask)		
Mask seems better (willingness to accept)	10 (8%)	36 (28%)
Injection is distressing/frightening (willingness to avoid)	12 (9%)	25 (20%)
Would have the injection if advised or had to	15 (11%)	18 (14%)
Like to have the choice	4 (3%)	11 (9%)
No experience of the injection	1 (0.5%)	5 (4%)

TABLE 76 *Reason given for preference for maintenance method in the paediatric study*

Reason given	No. of parents/guardians	
	Propofol/ halothane (*n* = 132)	**Sevoflurane/ sevoflurane (*n* = 128)**
Less chance of being sick	112 (85%)	109 (85%)
It is distressing being sick	4 (3%)	6 (5%)
Sickness does not last as long	2 (2%)	1 (0.5%)
Son/daughter was sick this time	1 (0.5%)	0 (0%)

feeling or being sick was quantified using willingness to pay (see chapter 5). Some respondents (4% propofol/halothane; 5% sevoflurane/sevoflurane) did not understand the question and only used the values offered on the VAS, and one respondent stated a protest value of £0. These values were excluded from the analysis in the empirical study.

Table 77 summarises the parents' or guardians' reasons for preferring maintenance with medicine D. The majority of parents' or guardians' stated willingness-to-pay value reflected how much they valued their child not being sick. Interestingly, some respondents felt that avoiding sickness was not as important as the choice between an injection or mask for the induction of anaesthesia.

Adult patients' views

A total of 85% (n = 907) of patients recruited into the empirical study were telephoned. Of these, 25% (n = 228) had received propofol induction and maintenance anaesthesia (propofol/propofol), 26% (n = 232) had received propofol induction and isoflurane maintenance anaesthesia (propofol/isoflurane), 26% (n = 234) had received propofol induction and sevoflurane maintenance anaesthesia (propofol/sevoflurane) and 23% (n = 213) had received sevoflurane induction and maintenance anaesthesia (sevoflurane/sevoflurane).

Which anaesthetic did I have?

The majority (85% propofol/propofol, 87% propofol/isoflurane, 89% propofol/sevoflurane, 89% sevoflurane/sevoflurane) of patients correctly recalled the type of induction anaesthetic they were given.

All patients in the empirical study would probably have received oxygen via a mask and had a cannula put in place prior to induction for safety reasons. This could explain the confusion by some patients who believed they had an injection and a mask when sent to sleep or mistakenly thought they were given an injection when they had a mask, or vice versa (3% propofol/propofol, 7% propofol/isoflurane, 5% propofol/sevoflurane, 4% sevoflurane/sevoflurane).

A minority (5% propofol/propofol, 1% propofol/isoflurane, 3% propofol/sevoflurane, 1% sevoflurane/sevoflurane) of patients were not sure which type of induction agent they had, and they said:

> "I went to sleep too quickly to remember".

Views on this anaesthetic

Table 78 summarises the patients' views about the anaesthetic received in the empirical study. Respondents were offered a choice of three possible answers to this question: pleasant, unpleasant or average.

Discomfort from injection or mask

More patients who had propofol/propofol (29%) said they experienced discomfort from the injection than those who had propofol/isoflurane (23%) or propofol/sevoflurane(19%). Of these

TABLE 77 *Reason given for willingness to pay for maintenance method in the paediatric study*

Reason given	No. of parents/guardians	
	Propofol/halothane (*n* = 132)	**Sevoflurane/sevoflurane (*n* = 128)**
Less chance of being sick (willingness to avoid)	71 (54%)	76 (59%)
Only pay more if zero chance of being sick with medicine D	18 (26%)	14 (11%)
Want the best one for my son/daughter (willingness to accept)	16 (12%)	11 (9%)
Medicine C and D are similar	4 (3%)	7 (5%)
This is not as important as the choice of induction agent	6 (5%)	2 (2%)
Being sick will prolong recovery	3 (2%)	3 (2%)

TABLE 78 *Views on the anaesthetic received in the adult empirical study*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	Propofol/isoflurane (*n* = 232)	Propofol/sevoflurane (*n* = 234)	Sevoflurane/sevoflurane (*n* = 213)
Pleasant	149 (65%)	160 (69%)	166 (71%)	120 (57%)
Unpleasant	23 (10%)	14 (6%)	17 (7%)	45 (21%)
Average	41 (18%)	47 (20%)	40 (17%)	39 (18%)
Not sure	15 (7%)	11 (5%)	11 (5%)	9 (4%)

patients, some referred to the experience of the propofol being administered. They reported slightly different feelings:

> "I could feel the cold going up arm, very uncomfortable" [agyfs105]

> "... hot warm sensation at time of injection, site still sore and swollen" [agyfa544].

Some patients referred to the discomfort associated with the cannula being put in place:

> "They couldn't find a vein and it was painful to get needle in" [agnfc069].

Around 1 in 5 patients said they experienced some discomfort with the mask (17% sevoflurane/sevoflurane). Some of these patients referred to the smell or taste of the sevoflurane:

> "No physical problems but I didn't like the smell and I could still smell and taste it next day" [agyfa764]

and some did not like the feeling of the mask being held down on their face:

> "The anaesthetist held the mask down and I didn't like it" [agyfa150].

Anaesthetic comparisons

The majority of patients (86% propofol/propofol, 82% propofol/isoflurane, 87% propofol/ sevoflurane, 85% sevoflurane/sevoflurane) had experienced a previous operation. These patients had undergone a wide variety of different procedures, from day procedures to hip replacement, spinal surgery and mastectomy.

Table 79 summarises the comparisons patients made with the anaesthetic they had in this study and previous anaesthetics experienced. Some patients may have mentioned more than one theme in their comparison.

Generally, the patients were clear which anaesthetic they preferred. However, some patients, especially those who were randomised to receive sevoflurane/sevoflurane, reported both positive and negative experiences:

> "Going to sleep was better, no sharp sting in my hand, but I was sick afterwards" [agnmc120]

> "I preferred the mask to go to sleep – I don't like the drunk feeling with the injection. I did feel really sick and had a severe headache though" [agyfa817].

Ready to leave hospital

The majority of patients (88% propofol/propofol, 85% propofol/isoflurane, 85% propofol/sevoflurane, 88% sevoflurane/sevoflurane) felt ready to go home when they did, as this one explained:

> "Yes, if I'd stayed an extra night I wouldn't have been any better" [agnmc196].

Some of the patients wanted to get home to their own environment, even though they may not have been feeling very well:

> "I felt I wanted to go home, but felt poorly. It was my decision to go home" [agyfs080].

However, some patients (7% propofol/propofol, 9% propofol/isoflurane, 9% propofol/sevoflurane, 8% sevoflurane/sevoflurane) said they would have preferred to stay in longer because they felt they needed more rest:

> "No, I felt very sleepy. I was not really aware and I can't remember leaving" [agyfa780]

or they felt they would not be able to cope at home:

> "To be honest I felt they should have kept me in for the first night. I have a young boy and my sister had to have him' [agyfs042].

A minority of the patients felt they were rushed out of the hospital:

TABLE 79 *Comparisons with previous anaesthetics in the adult study*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	**Propofol/isoflurane (*n* = 232)**	**Propofol/sevoflurane (*n* = 234)**	**Sevoflurane/sevoflurane (*n* = 213)**
Can't remember	26 (11%)	17 (7%)	26 (11%)	25 (12%)
No difference	41 (18%)	48 (21%)	54 (23%)	34 (16%)
Less drowsy with this one	31 (14%)	27 (12%)	26 (11%)	20 (9%)
More drowsy with this one	10 (4%)	9 (4%)	7 (3%)	13 (6%)
Less sick with this one	33 (14%)	31 (13%)	31 (13%)	21 (10%)
More sick with this one	11 (5%)	15 (6%)	10 (4%)	14 (7%)
This one was 'the best'	22 (10%)	22 (9%)	23 (10%)	16 (8%)
Last one was 'the best'	0 (0%)	3 (1%)	2 (1%)	6 (3%)
Less frightened/crying/ emotional after this one	7 (3%)	6 (3%)	8 ()3%	3 (1%)
More frightened/crying/ emotional after this one	3 (1%)	2 (1%)	2 (1%)	5 (2%)
Less sore throat/cough after this one	6 (3%)	1 (0.5%)	2 (1%)	0 (0%)
More sore throat/cough after this one	0 (0%)	3 (1%)	1 (0.5%)	4 (2%)
Less headache after this one	3 (1%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
More headache after this one	2 (1%)	2 (1%)	6 (3%)	8 (4%)
Less pain with this one	1 (0.5%)	7 (3%)	7 (3%)	10 (5%)
More pain with this one	10 (4%)	9 (4%)	8 (3%)	0 (0%)
Last one took longer to send me to sleep	3 (1%)	7 (3%)	4 (2%)	1 (0.5%)
This one took longer to send me to sleep	3 (1%)	1 (0.5%)	1 (0.5%)	7 (3%)
Less able to concentrate after this one	2 (1%)	0 (0%)	2 (1%)	2 (1%)
Breathless after this one	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Had a mask (oxygen) with this one	1 (0.5%)	2 (1%)	1 (0.5%)	0 (0%)
Tasted the gas with this one	0 (0%)	4 (2%)	3 (1%)	3 (1%)
Did not like the gas/ prefer the injection	0 (0%)	0 (0%)	0 (0%)	20 (9%)
Prefer the gas	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Had a rash after this one	2 (1%)	0 (0%)	0 (0%)	0 (0%)

> "No, I felt rushed. I was in a lot of pain/discomfort – had to walk to the car. I had been told I'd be given a wheelchair" [agnfc061].

Some patients (4% propofol/propofol, 5% propofol/isoflurane, 6% propofol/sevoflurane, 3% sevoflurane/sevoflurane) felt they were kept in the hospital too long and felt ready to go home earlier than they did:

> "Yes, I did actually, I was ready before I went. I was held back as staff were busy" [agyfa882].
>
> 'I was ready to go earlier – waiting for discharge papers and sick note but I understood why" [agnmc169].

Satisfaction with care

Overall (99%), the patients were very satisfied with the care they received on the ward before their operation. Satisfaction with preoperative care was not dependent on the type of anaesthetic they had received. Those patients who were not happy referred to being unsettled by the wait before their operation:

> "Not really – left in recovery waiting before the operation on own. I was cold and alone and I got upset" [agyfs001].
>
> "There was a very long delay – about 2 hours – that was very unsettling" [agnmc010].

A slightly lower proportion of patients (97% propofol/propofol, 95% propofol/isoflurane, 96% propofol/sevoflurane, 98% sevoflurane/sevoflurane) were satisfied with the care they received in the recovery area after their operation. Those patients who were not happy referred to poor communication by the staff:

> "Not really – I was really drowsy, had to ask for someone to give the diagnosis. There was poor communication from the doctors – no explanation of treatment" [agyfs001].
>
> "Yes – except the news wasn't good but I felt it wasn't appropriate for Mr xxx to tell me the bad news in recovery and not to see me on the ward afterwards. That's why I felt I had to ring and clarify what was said" [agyfa1119].

This patient was not happy with the level of pain control they received:

> "Not really no – I think there was not a lot of care – they put me on the bed and left me in pain" [agyfs055].

A similar proportion of patients (96% propofol/propofol, 93% propofol/isoflurane, 93% propofol/sevoflurane, 96% sevoflurane/sevoflurane) were satisfied with the care they received after their operation on the ward. Those patients who were not happy about their care made comments about the staff or the service regarding communication or discharge delays:

> "No, in the day ward the nurses were moaning about each other all the time, they were too busy concentrating on the next day's work. I felt I was a nuisance" [agnfc010].
>
> "Yes OK but the doctor was very abrupt in terms of how he told me about my potential treatment and dealt with me on the ward" [agyfs062].
>
> "... bit of delay (to go home) – waiting for the tablets from pharmacy" [agyfa256].
>
> "I was left waiting for transport for 11/2 hrs because someone forgot it" [agnmc027].

Days to recover after the operation

The patients were asked to recall how many days it took them to recover from the operation and resume their normal activities. About 1 in 10 patients (11% propofol/propofol, 12% propofol/isoflurane, 16% propofol/sevoflurane, 13% sevoflurane/sevoflurane), who were telephoned, were not able to answer this question. No difference was seen between three of the groups (propofol/propofol, propofol/isoflurane, sevoflurane/sevoflurane). On average, the patients felt it took 5 days (95% CI, 4.2 to 5.9 propofol/propofol; 95% CI, 4.3 to 5.7, propofol/isoflurane; 95% CI, 4.3 to 5.9, sevoflurane/sevoflurane) for them to recover from their operation. The propofol/sevoflurane group felt it took an average of 6 days (95% CI, 5.1 to 6.9) for them to recover from their operation.

Adult patients' preferences for induction

Table 80 summarises the reasons why patients would prefer the injection (medicine A) or the mask (medicine B) to send them to sleep for a future day procedure (see chapter 6 for the overall number who preferred medicine A or B).

The majority of patients who preferred the injection to the mask for a future induction explained this was because they were frightened of the mask:

> "... because I think the injection is quicker and I can imagine wanting to kick a person holding the mask over my face, off me" [aorfc011].

Patients who had had the mask in the empirical study had some concerns and were likely to prefer an injection in future:

TABLE 80 *Reason given for preference for induction method in the adult study*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	**Propofol/isoflurane (*n* = 232)**	**Propofol/sevoflurane (*n* = 234)**	**Sevoflurane/sevoflurane (*n* = 213)**
Preference for medicine A (injection)				
Mask is distressing/ frightening	70 (31%)	74 (32%)	89 (38%)	25 (12%)
Bad previous experience of the mask (e.g. at the dentist)	13 (6%)	26 (11%)	16 (7%)	2 (1%)
The injection works quicker	15 (7%)	15 (6%)	17 (7%)	7 (3%)
Did not experience the pain described	13 (6%)	21 (9%)	13 (6%)	3 (1%)
The injection is fine	17 (7%)	15 (6%)	15 (6%)	5 (2%)
No experience of the mask	22 (10%)	17 (7%)	17 (7%)	0 (0%)
The gas makes me sick	2 (1%)	7 (3%)	1 (0.5%)	10 (5%)
Do not like the smell/taste of the gas	4 (2%)	7 (3%)	5 (2%)	10 (5%)
Less drowsy with the injection	2 (1%)	3 (1%)	4 (2%)	0 (0%)
Feel safer/more asleep with the injection	2 (1%)	0 (0%)	1 (0.5%)	2 (1%)
Preference for medicine B (mask)				
Injection is painful	29 (13%)	33 (14%)	27 (12%)	67 (31%)
The mask sounds better as described	6 (3%)	5 (2%)	8 (3%)	49 (23%)
Less drowsy with the mask	4 (2%)	0 (0%)	2 (1%)	6 (3%)
The mask works quicker	3 (1%)	1 (0.5%)	0 (0%)	6 (3%)
The mask smells sweet	0 (0%)	1 (0.5%)	0 (0%)	3 (1%)
Never had the injection	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Injection is distressing/ frightening	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Liked the mask at the dentist	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)

> "I don't like the smell of the gas, reminds me of the dentist" [agyfa850].

Patients who preferred the mask in future said they thought the injection was painful:

> "... because the injection was painful and I was very surprised" [agyfa504]

or they clearly felt the mask was better for them:

> "... because I have control. I was a little dubious before but I was amazed how good it was" [agyfa1126].

Patients' strength of preference for induction of anaesthesia with an injection or a mask was quantified using willingness to pay (see chapter 6). The respondents were asked to explain why they stated the value they did and the majority seemed to understand the concept of willingness to pay. However, some respondents (12% propofol/ propofol, 7% propofol/isoflurane, 10% propofol/ sevoflurane, 11% sevoflurane/ sevoflurane) did not understand the question and only used the available values on the VAS:

> "I treated the scale like it was out of 10" [agyfs083, willingness to pay £150].

Five patients gave protest values and said:

> "I won't pay on principle – healthcare should be free at point of delivery" [agyfa1063, willingness to pay £0].

These values (12% propofol/propofol, 8% propofol/isoflurane, 10% propofol/sevoflurane, 12% sevoflurane/sevoflurane) were excluded from the main analysis of the willingness-to-pay values (see chapter 6).

Table 81 shows the reasons patients gave for their stated willingness-to-pay values. Patients mainly said they were stating their strength of preference for avoiding the mask or injection:

> "I really do not like needles and would do a lot to avoid one" [agnmc147, willingness to pay £250]

or indicating how much they wanted the mask or injection:

> "... because I am expressing my high satisfaction with treatment" [agnmc043, willingness to pay £200].

Some patients did not have a strong preference for the method of induction and would have the other option if that was offered:

> "... because although I have a minor preference, it is minor and if I had to have the other then I would" [agyfa161, willingness to pay £25].

Some patients did not give a reason, but said their valuation reflected their strength of preference for the chosen method of induction:

> "... because that's my personal feeling about how much I'd prefer medicine A" [agyfs042, willingness to pay £250].

Adult patients' preferences for maintenance

Table 82 summarises the reasons behind the patients' stated preference for medicine D compared to medicine C for the maintenance of anaesthesia. The majority of patients chose medicine D, which offered them less chance of feeling or being sick. Three per cent of all respondents (4% propofol/propofol, 2% propofol/isoflurane, 4% propofol/sevoflurane, 2% sevoflurane/sevoflurane) stated a preference for medicine C and a further two respondents did not state a preference because they did not understand the question. The associated willingness-to-pay values were excluded from the analysis in the empirical study.

Generally patients chose medicine D because they identified there was less chance of being sick:

> "... because 7/10 feel sick with C and 3/10 feel sick with D" [agyfa1104].

Some patients felt strongly that they did not want to be sick:

> "Want best chance – being sick is horrible" [aormc076].

Patients' strength of preference for maintenance of anaesthesia with a lower chance of feeling or being sick was quantified using willingness to pay (see chapter 4). Some respondents (7% propofol/propofol, 6% propofol/isoflurane, 6% propofol/sevoflurane, 7% sevoflurane/sevoflurane) did not understand the question and used the values like a VAS and five respondents stated a protest value of £0. These values were excluded from the analysis in the empirical study. *Table 83* shows the reasons given for the stated willingness-to-pay values.

Patients' strength of preference for medicine D reflected that they did not like being sick:

> "If it makes me feel less sick I'd put a lot of value on that. I felt really sick" [agnmc007, willingness to pay £250].

Interestingly, most patients said they did not value not being sick as strongly as their choice of induction agent:

> "I do not think it is as important, feeling sick. It is not something I am scared of and I could put up with it" [agyfs032, willingness to pay £100].

Concluding remarks

Overall, parents, guardians or patients were more likely to prefer the anaesthetic technique they experienced in the empirical study than anaesthetics they, or their child, may previously have received.

The parents' and guardians' views and experiences with the anaesthetics given to their children in this study were very similar between the two treatment arms. The main difference was that they were more likely to have observed their child having propofol induction in the past and their son/daughter seemed less drowsy after this operation than in previous experiences. Most patients, and parents or guardians, were extremely satisfied with the

TABLE 81 *Reason given for willingness to pay for induction method in the adult study*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	**Propofol/isoflurane (*n* = 232)**	**Propofol/sevoflurane (*n* = 234)**	**Sevoflurane/sevoflurane (*n* = 213)**
Willingness-to-pay for medicine A (injection)				
The mask is distressing/ frightening (willingness to avoid)	52 (23%)	70 (30%)	53 (23%)	16 (8%)
The injection seems better (willingness to accept)	39 (17%)	34 (15%)	37 (16%)	9 (4%)
No strong preference – would have the mask	45 (20%)	39 (17%)	49 (21%)	14 (7%)
Felt better afterwards with the injection compared to the mask	3 (1%)	10 (4%)	4 (2%)	9 (4%)
Like to have the choice	3 (1%)	4 (2%)	2 (1%)	2 (1%)
No experience of the mask	7 (3%)	8 (3%)	14 (6%)	0 (0%)
This amount reflects my preference for the injection	7 (3%)	5 (2%)	9 (4%)	3 (1%)
Mask takes longer to go to sleep	4 (2%)	2 (1%)	4 (2%)	2 (1%)
Did experience some pain, but still prefer the injection	2 (1%)	1 (0.5%)	1 (0.5%)	0 (0%)
Bad experience at the dentist	0 (0%)	5 (2%)	1 (0.5%)	0 (0%)
Feel more asleep with the injection	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Do not like the smell of the mask	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Willingness to pay for medicine B (mask)				
The mask seems better (willingness to accept)	11 (5%)	3 (1%)	5 (2%)	36 (17%)
Injection is distressing/ frightening (willingness to avoid)	11 (5%)	9 (4%)	8 (3%)	23 (11%)
Would have the injection if advised or had to	17 (7%)	24 (10%)	20 (9%)	55 (26%)
Like to have the choice	0 (0%)	2 (1%)	1 (0.5%)	5 (2%)
No experience of the injection	0 (0%)	1 (0.5%)	2 (1%)	3 (1%)
Do not want the mask really, but would have it rather than the pain	1 (0.5%)	0 (0%)	1 (0.5%)	2 (1%)
This amount reflects my preference for the injection	1 (0.5%)	1 (0.5%)	2 (1%)	2 (1%)

TABLE 82 *Reason given for preference for maintenance method in the adult study*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	Propofol/isoflurane (*n* = 232)	Propofol/sevoflurane (*n* = 234)	Sevoflurane/sevoflurane (*n* = 213)
Less chance of being sick (willingness to avoid)	178 (78%)	196 (84%)	180 (77%)	166 (78%)
It is distressing being sick (willingness to avoid)	15 (7%)	13 (6%)	20 (9%)	27 (13%)
Sickness does not last as long with medicine D	5 (2%)	2 (1%)	3 (1%)	1 (0.5%)
No preference really	1 (0.5%)	1 (0.5%)	3 (1%)	3 (1%)

TABLE 83 *Reason given for willingness to pay for maintenance method*

View on anaesthetic	No. of patients			
	Propofol/propofol (*n* = 228)	Propofol/isoflurane (*n* = 232)	Propofol/sevoflurane (*n* = 234)	Sevoflurane/sevoflurane (*n* = 213)
I do not like being sick	74 (32%)	97 (42%)	98 (42%)	86 (40%)
This is not as important as the choice of induction agent	50 (22%)	46 (20%)	28 (12%)	30 (14%)
Less chance of being sick (willingness to avoid)	39 (17%)	41 (18%)	44 (19%)	33 (15%)
Only pay more if zero chance of being sick with medicine D	8 (4%)	6 (3%)	16 (7%)	17 (8%)
I want the best one (willingness to accept)	8 (4%)	8 (3%)	16 (7%)	11 (5%)
Medicines C and D are similar	9 (4%)	9 (4%)	12 (5%)	9 (4%)
Being sick will prolong recovery	13 (6%)	2 (1%)	3 (1%)	6 (3%)

care they, or their child, received during the day procedure.

Adult patients' views and experiences with the anaesthetics used in this study were similar between the four treatment arms, except for those patients who had sevoflurane induction. Some of these patients expressed a strong dislike for this anaesthetic technique. Some adult patients reported discomfort when propofol was administered for the induction of anaesthesia. However, some of the adult patients who received sevoflurane for induction reported fear of the mask and did not like the taste or smell of the gas.

Exploring the reasons behind parents' or guardians' and patients' direction and strength of preference for induction and maintenance anaesthetic agents indicated that the majority of respondents understood the purpose of the willingness-to-pay valuation exercise. The willingness-to-pay values of those parents or guardians and patients who did not seem to understand the question were excluded from the analysis in the empirical study.

Patients and children who did not experience the mask in this empirical study tended to say they would find it distressing and preferred the injection. However, the majority of patients who did have the mask said they would have it again in the future and they preferred it. Some patients preferred the mask because they felt the injection was painful. Generally, patients' strength of preference for induction agent seemed stronger than that for the maintenance agent.

Appendix 17

Calculating variable costs

Background

Variable costs account for resource use that changes with respect to output. Drug and disposable equipment are some examples of variable costs associated with anaesthesia for a day procedure. The empirical study required information on these variable costs.

Method

The types of variable cost data collected were:

- anaesthetic use
- all drug use during anaesthesia
- PONV and adverse-event management
- anaesthetic room resource use
- theatre resource use
- recovery room resource use
- ward resource use
- postdischarge NHS resource use.

Drug and anaesthetic variable costs

Variable costs were collected prospectively. The name, form, strength and quantity of all drugs, including take-home drugs, given to each patient throughout the day procedure were recorded. This included drugs used in the management of PONV. Changes in fresh gas (oxygen or N_2O) flows and volatile anaesthetic concentrations, made by the anaesthetist, to prevent or react to adverse events were also recorded.

The quantity of volatile anaesthetic and fresh gases given to each patient was calculated using the Dion approximation.[24] This requires information on the concentrations and flow rates used throughout the induction and maintenance of anaesthesia. Concentration and flow rate were recorded at regular intervals: 1-minute intervals in the anaesthetic room; 1-minute intervals for the first 10 minutes, then 2-minute intervals for a further 10 minutes and then 5-minute intervals in the operating theatre.

Adverse-event management variable costs

The variable costs associated with the management of adverse events were collected for the anaesthetic room, theatre, recovery and the ward. The type of adverse event and the quantity of resources used to manage each adverse event were recorded. Only anaesthetic-related adverse events were included, surgical adverse events being excluded. Some examples of event-associated resource use include: the insertion of a new laryngeal mask; a visit from a senior anaesthetist to manage an adverse event; and the patient vomited.

Posthospital resource use variable costs

Postdischarge NHS resource use data were collected during the telephone interview with the patient or the patient's parent or guardian at day 7 postdischarge. Three categories of posthospital resource use were identified:

- over-the-counter medicines bought
- visit or contact with a GP and associated prescribed drug costs
- visit or contact with the hospital.

Over-the-counter medicines bought

The over-the-counter medicines bought were not consistent with the study perspective and were not included in the total variable cost. However, the type of over-the-counter medicines bought by each patient was recorded to provide information about the use of community-based healthcare services (community pharmacies) following a day procedure.

GP visit

A visit to a GP was categorised into one of five types:

- the patient consulted with the GP
- the patient telephoned the GP
- the patient telephoned the surgery and spoke to the receptionist
- the patient consulted with the practice nurse
- the patient had a home visit by a district nurse.

Hospital visit

There were four categories of hospital 'visit':

- the patient attended the accident and emergency department
- the patient was admitted for an overnight stay

- the patient had an outpatient appointment with the consultant
- the patient telephoned the ward for advice.

Unit cost data

Unit costs for the year 2000 were attached to the resource use. For hospital resource use the NHS trust specific unit cost data were obtained for drugs, disposable items and sundries, from pharmacy and supplies departments. There was little variation between the unit costs for drugs and supplies between the two NHS trusts. The unit costs from one of the two NHS trusts was used in the baseline analysis.

Table 84 summarises the unit cost data for the management of adverse events. For the management of adverse events a unit cost of zero was attached if:

- no action was taken
- drugs or fluids were given (because these were already recorded and valued in 'drug costs')
- there was a change in fresh gas flows or volatile anaesthetic concentration (because these were already recorded and valued in 'anaesthetic costs')
- the patient had an overnight stay (because these were already recorded and valued in 'overnight stay')
- the patient was kept on the ward longer (because these were already recorded and valued in 'length of stay')
- the patient developed laryngospasm or hyperventilation (the patient would have been monitored but the action taken did not incur cost)
- the patient had excessive salivation (routine suction would have been used but the action taken did not incur cost)
- the patient bled from the wound (extra pressure would have been applied to existing dressings but the action taken did not incur cost).

The unit cost of the smallest pack size of the over-the-counter medicine was used to cost medicines bought. *Table 85* summarises these unit cost data.

Each category of a GP 'visit' was assigned a unit cost (*Table 86*), which reflected the time to complete the 'visit' and the value, in terms of the average salary per minute of the person involved. The costs were obtained from a published source and included the discounted value of training the healthcare professional concerned.[244] The cost of consulting a receptionist was valued by assuming the average UK salary.[245] The cost of drugs prescribed by the GP was valued using the *British National Formulary* drug price, inclusive of VAT, for a course of the named drugs, one tube of cream or 1 week's supply for maintenance therapy (*Table 87*). Some drugs were not specifically named, but the class of drug (e.g. antibiotic) was recorded. In this situation an assumption was made regarding the name of the drug and the appropriate dose using the *British National Formulary* (e.g. amoxicillin 250 mg capsules for 5 days).

Each category of hospital visit was assigned a unit cost from a published source (*Table 88*).[244] The cost of a telephone consultation was valued assuming an E grade nurse took the call lasting 10.8 minutes.

Total variable cost

The total variable cost for hospital resource use (i.e. the sum of drug, anaesthetic and adverse-event variable costs) was calculated per patient. The total variable cost was used in the baseline analysis of the economic evaluation. The cost of posthospital resource use was reported separately. The posthospital resource cost excluded the cost of the patient purchasing over-the-counter medicines.

TABLE 84 *Unit costs for the management of adverse events*

Management of adverse events	Unit	Unit cost (£)
New laryngeal mask inserted	Cost of laryngeal mask/number of times re-used (40) + processing costs	2.92
Visit by surgeon or anaesthetist due to adverse event	10.8 minute x salary + contributions	7.24
Patient vomited	Laundry costs (sheets, pillow case, gown) + vomit bowl	0.94

TABLE 85 *Unit costs for the purchase of over-the-counter medicines by patients*

Over-the-counter product (generic medicine)	Unit	Unit cost[243] * (£)
Anadin Extra® (aspirin)	8 tablets	0.99
Anadin Soluble® (aspirin)	8 tablets	1.19
Clarytin® (loratidine)	7 tablets	4.25
Cocodamol	32 tablets	1.50
Cuprofen® (ibuprofen)	12 tablets	1.45
'Dressing' Melolin®	5 dressings	1.05
Feminax®	20 tablets	2.49
Ibuprofen	16 x 200 mg tablets	1.30
Junior Disprol® (paracetamol)	16 tablets	1.25
Kaolin and morphine	200 mls	1.75
Motilum® (domperidone)	10 tablets	3.95
Nurofen® (ibuprofen)	12 tablets	1.59
Paracetamol	16 tablets	0.29
Paracodol® (paracetamol, codeine)	12 tablets	1.99
Paramol® (paracetamol, dihydrocodeine)	24 tablets	3.99
Peptobismol®	120 mls	2.99
Potassium citrate	200 mls	1.22
Propain® (paracetamol, codeine, diphenhydramine)	12 tablets	2.30
Rennies®	8 tablets	0.61
Solpadol® (paracetamol, codeine)	12 tablets	2.25
Strepsils®	24 lozenges	2.05

* *Personal communication. Manchester: High Street Pharmacy, 2000*

TABLE 86 *Unit costs of a GP visit*

Visit type	Unit	Unit cost (£)
District nurse visit	Per home visit	19.00
GP clinic consultation	Per consultation of 9.36 min	17.00
GP home visit	Per home visit of 13.2 min and 12 min travel time	42.00
GP receptionist consultation	Per consultation of 10.8 min	1.85
GP telephone consultation	Per consultation of 10.8 min	20.00
Health visitor	Per home visit	29.00
Practice nurse visit	Per consultation	9.00
Practice nurse visit	Per home visit	17.00

TABLE 87 *Unit costs of drugs prescribed by a GP*

Drug prescribed	Unit	Unit cost (including VAT) (£)
'Antibiotic cream', mupiprocin 2%	15 g	4.28
'Antibiotics', amoxicillin 250 mg	15 capsules	2.66
Cefalexin 250 mg	20 capsules	2.77
Ciprofloxacin 250 mg	14 tablets	12.34
Cocodamol	20 tablets	1.80
Codeine phosphate 30 mg	20 tablets	1.80
Codydramol	20 tablets	0.60
Coproxamol	20 tablets	0.40
Diclofenac 50 mg	21 tablets	1.68
Dihydrocodeine 30 mg	20 tablets	1.40
'Ear spray', Sofradex®	10 mls	6.12
Erythromycin 250 mg	28 tablets	3.62
Flucloxacillin 250 mg	20 capsules	3.03
Hormone replacement therapy, Prempak C® 0.625	7 tablets	1.01
Ibuprofen 400 mg	21 tablets	1.48
Lignocaine 2%	20 g	1.25
Medroxyprogesterone 10 mg	7 tablets	2.03
Metronidazole 400 mg	21 tablets	5.86
'Migraine beta blockers', Propranolol 40 mg	21 tablets	0.12
Norethisterone 5 mg	21 tablets	1.78
'Painkillers', Co-codamol	20 tablets	1.80
Penicillin V 500 mg	28 tablets	2.40
Ponstan® 500 mg	21 tablets	2.01
'Steroid cream', hydrocortisone 1%	15 g	0.49
Trimethoprim 100 mg	7 tablets	0.17

TABLE 88 *Unit costs of a hospital visit*

Visit type	Unit	Unit cost (£)
Accident and emergency visit	Per outpatient attendance	65.00
Inpatient stay	Per inpatient day	223.00
Outpatient attendance	Per outpatient attendance	68.00
Phone call to hospital	Per phone call (10.8 min)	5.58

Appendix 18

Determining the quantity of the volatile anaesthetic agents used

Background

The empirical study required accurate and detailed information on the quantities of anaesthetic used. For volatile anaesthetics, it is not possible to measure the quantity administered in terms of volume. The carrier gases, normally oxygen and N_2O, pass through an agent-specific vaporiser mounted on the anaesthetic machine in which the liquid anaesthetic agent is vaporised and added to the stream of gases. The combination of gases and anaesthetic vapour is carried to and from the patient's lungs by a system of tubing known as the 'breathing system'. The vaporisers used to administer volatile anaesthetics are calibrated to show the percentage concentration of vapour delivered to the breathing system rather than the volume of liquid agent delivered in millilitres. The anaesthetist intermittently varies the concentration of agent delivered to the breathing system by adjusting the dial on the vaporiser according to the needs of the patient. The volume of liquid agent delivered to the patient depends, *inter alia*, on the flow of carrier gases passing through the vaporiser (known as the 'fresh gas flow') and the percentage concentration of vapour set on the vaporiser dial.

The type of breathing system is relevant to the economy with which the anaesthetic agent is utilised. There are broadly two types. In a non-re-breathing system, a large flow of anaesthetic gases and vapour is carried to the patient's lungs. An amount of anaesthetic agent and oxygen is taken up by the patient and the remainder is vented to the atmosphere. In a re-breathing system the 'waste' gases and vapour exhaled by the patient are recycled continuously by immediately directing the exhaled breath through a low-resistance carbon dioxide-absorbing canister and thence back to the patient. This system is commonly described as a 'circle system'. All that has to be added to a circle system is the amount of oxygen (approximately 200 ml/min) and the amount of anaesthetic vapour actually taken up by the patient with each breath. The predominant advantage of reducing the fresh gas flow to a minimum is extreme economy of use. A second advantage is the considerable reduction in the release of N_2O and anaesthetic halogenated hydrocarbons into the atmosphere. A potential disadvantage is that it is difficult rapidly to vary the amount of anaesthetic agent available to the patient if, for example, the severity of the surgical stimulus suddenly increases and it becomes necessary to quickly deliver more anaesthetic to the patient to avoid excessively light anaesthesia. In these circumstances it is usual to increase the fresh gas flow for a few minutes in addition to increasing the vaporiser setting. During the first few minutes of anaesthesia, the uptake of anaesthetic agent by the patient's tissues is very high. In order to provide sufficient anaesthetic agent, a relatively high fresh gas flow is required initially and, subsequently, the flow is progressively decreased by the anaesthetist. To ensure that the appropriate anaesthetic concentration is achieved in the circle breathing system, the actual percentage of vapour being delivered to the patient is routinely measured on a breath-by-breath basis throughout each anaesthetic using an accurate monitor. In practice, circle systems are seldom used in their most parsimonious 'closed' state and a fresh gas flow is chosen which achieves the best compromise between economy on the one hand and the ability to vary the amount of anaesthetic agent available to the patient on the other.

Previous studies have attempted to estimate the cost of anaesthetic agents by simply measuring the volume of liquid agent used.[22] Weighing the vaporiser containing the volatile anaesthetic before and after anaesthesia is the most accurate way to calculate the quantity of volatile anaesthetic agent used.[28] However, this process is logistically demanding and time consuming and was considered on these grounds to be inappropriate for the large numbers of patients recruited to the current study. The Dion formula was developed and has been used in several studies to estimate the quantity and cost of volatile anaesthetic agents administered using machines with no system to allow re-breathing of the vapours.[24,220] The widespread introduction of circle systems into anaesthetic practice[246] has generated some uncertainty in the CESA team of investigators

concerning the accuracy of the Dion calculation, because exhaled anaesthetic vapour is recycled rather than being vented to the atmosphere. It was surmised that the Dion formula might overestimate (or underestimate) the quantity of liquid anaesthetic agent used during anaesthesia when a circle (re-breathing) system is employed.

The Dion formula estimates the quantity and cost of volatile anaesthetic used, as follows:

$$\text{Cost} = \frac{PFTMC}{2412\ d}$$

where P is the concentration of the vaporiser (%), M is the molecular weight (g), F is the fresh gas flow (l/min), T is the duration of anaesthesia (minute), C is the cost per millilitre (£/ml) and d is the density (g/ml). The formula suggests that 1 ml of liquid volatile agent produces approximately 200 ml of saturated vapour, or approximately 10 litres of anaesthetic vapour, at a fresh gas concentration of 2%.

A substudy was required to validate the Dion formula for estimating the amount of volatile anaesthetic used. Hereafter this substudy will be referred to as the 'volatile study'. The aim of the volatile study was to validate the Dion calculation, which was the method used to estimate the amount of anaesthetic used in the CESA RCT.

The objective of the volatile study was to compare the mass of each selected volatile anaesthetic used in the anaesthetic room or operating theatre calculated by weighing the vaporisers before and after surgery (true weight) with the estimated amount found by using the Dion calculation (estimated weight). The mass of volatile anaesthetic found by weighing the vaporisers was assumed to be the gold standard with which to compare the accuracy of the Dion formula.

Method

The key research question was whether the Dion formula gives valid and robust estimates of the amount of volatile anaesthetic used during a day-case surgical procedure.

The amount of volatile anaesthetic used was measured from the time the patient entered the anaesthetic room and the vaporiser was turned on to when maintenance of anaesthesia ended and the vaporiser was turned off. Data were collected for three types of volatile anaesthetic used in the main study: halothane, isoflurane and sevoflurane.

The vaporisers located in the anaesthetic room and operating theatre were weighed before and after every patient on days identified for data collection. The data collected on the amount of volatile anaesthetic used in the anaesthetic room was recorded separately from the data collected for the amount used in theatre. The weighing instrument was a Metler-Toledo SG high-capacity precision balance (model SG16000). The SG16000 has a maximum capacity of 16,000 g with an accuracy of 0.1 g.

The weighing process involved detaching the vaporiser from the back bar of the anaesthetic machine. To maximise the safety of anaesthetic and research staff the balance was kept on a theatre trolley and moved to the vaporiser, rather than the vaporiser being carried to the balance. The vaporiser was replaced immediately after it was weighed. It was assumed that there was no vapour loss when the vaporiser was detached from the anaesthetic circuit.

Study sample

The study sample was drawn from patients recruited for the main study. Weighing the vaporisers was logistically demanding and time consuming and the project coordinator identified specific days on which to weigh the vaporisers. The study population was a convenience subsample of the randomly sampled main study population.

Calibration

All vaporisers located in the theatres used in the volatile study had a current certificate of calibration issued by the vaporiser manufacturer. In addition, each vaporiser was calibrated separately. The vaporiser was put on an anaesthetic machine and a circuit established so the sampling system read the concentration of volatile anaesthetic from the common gas outlet. Each vaporiser was then turned on at three predefined concentration settings and two predefined flow rates of fresh gas. The concentration of inspired gas was then read from the anaesthetic machine monitor and used as an estimate of the accuracy of each setting on the vaporiser. All calibrations for the vaporiser readings were found to be within 10%.

The weighing instrument performs a self-calibration each time it is switched on.

Ethical approval

This was covered by the ethical approval obtained for the empirical study.

Analysis

In 1986, Bland and Altman[247] presented a statistical method for assessing the agreement between two methods of clinical measurement. This approach was used to determine the 'limits of agreement' between the Dion estimate and the weight of volatile anaesthetic. The limits of agreement are defined by the formula:

Lower limit of agreement = (mean of the difference) – (2 SD of the difference)

Upper limit of agreement = (mean of the difference) + (2 SD of the difference)

where

Difference = true weight – Dion weight (g)

The limits of agreement were used to determine how closely the two methods of quantifying the weight of volatile anaesthetic agreed. The acceptable range of the limits of agreement (within 10%) was predefined to establish if the two methods of quantifying the weight of volatile anaesthetic are similar enough to use the two methods interchangeably.

The limits of agreement for isoflurane and sevoflurane used in the anaesthetic room and theatre were calculated separately. There were no data on the use of halothane and sevoflurane in paediatric patients.

The Bland and Altman method of analysis does not provide any information on the correction factor that must be applied to the Dion estimate for it to match the true weight of volatile anaesthetic.

Results

The quantity of volatile anaesthetic used was weighed for 42 patients who were recruited for the empirical study (3 for halothane, 10 for isoflurane, 29 for sevoflurane). It was not feasible to analyse data for halothane as the number of cases weighed was small. The analysis focused on the data for isoflurane and sevoflurane.

The Dion formula generally underestimated the weight of isoflurane and sevoflurane in the anaesthetic room and operating theatre (*Figures 28* to *31*). The limits of agreement for isoflurane and sevoflurane, which are also shown on the graphs, are given in *Table 89*. The limits of agreement for these data were not sufficient (not within 10%) to assume that the Dion estimate and true weight could be used interchangeably.

This analysis confirmed that the Dion formula tended consistently to underestimate the quantity of volatile anaesthetic used. It was not possible to estimate formally a correction factor for the Dion formula because of the small sample size in this substudy. However, at this stage it is possible to calculate the mean difference between the Dion estimate and the true weight of volatile anaesthetic used (*Table 90*). The percentage mean difference (shown in the last column of *Table 90*) was used to indicate the average magnitude of the difference between the Dion estimate and the actual weight of anaesthetic.

The time over which the volatile anaesthetic was administered to the patient was recorded for each procedure in the anaesthetic room and theatre (*Table 91*). *Figures 32* and *33* show that the difference between the true weight and the estimated weight was not constant over the passage of time for each volatile anaesthetic. It was not possible formally to estimate the influence of time on the difference between the true weight and the weight estimated by means of the Dion formula because of the small sample size in this substudy.

Implications for the empirical study

The Dion formula was used in the baseline analysis of the empirical study because the published literature suggested this was the most valid means to estimate the quantity of volatile anaesthetic used without weighing each vaporiser used to administer the volatile anaesthetic to a patient. However, this substudy has shown that the Dion formula consistently underestimated the quantity of volatile anaesthetic used. There were insufficient data in this substudy to create an adjusted Dion estimate. A larger study with more patients was required. Results from this study suggested that the actual amounts of isoflurane and sevoflurane were between 6% and 27% higher than estimated, respectively. A sensitivity analysis of the Dion formula was used in the empirical study (see chapter 5) to illustrate the extent to which changing the quantity of volatile anaesthetic used would have an effect on the rank order of the ICERs for each anaesthetic agent used.

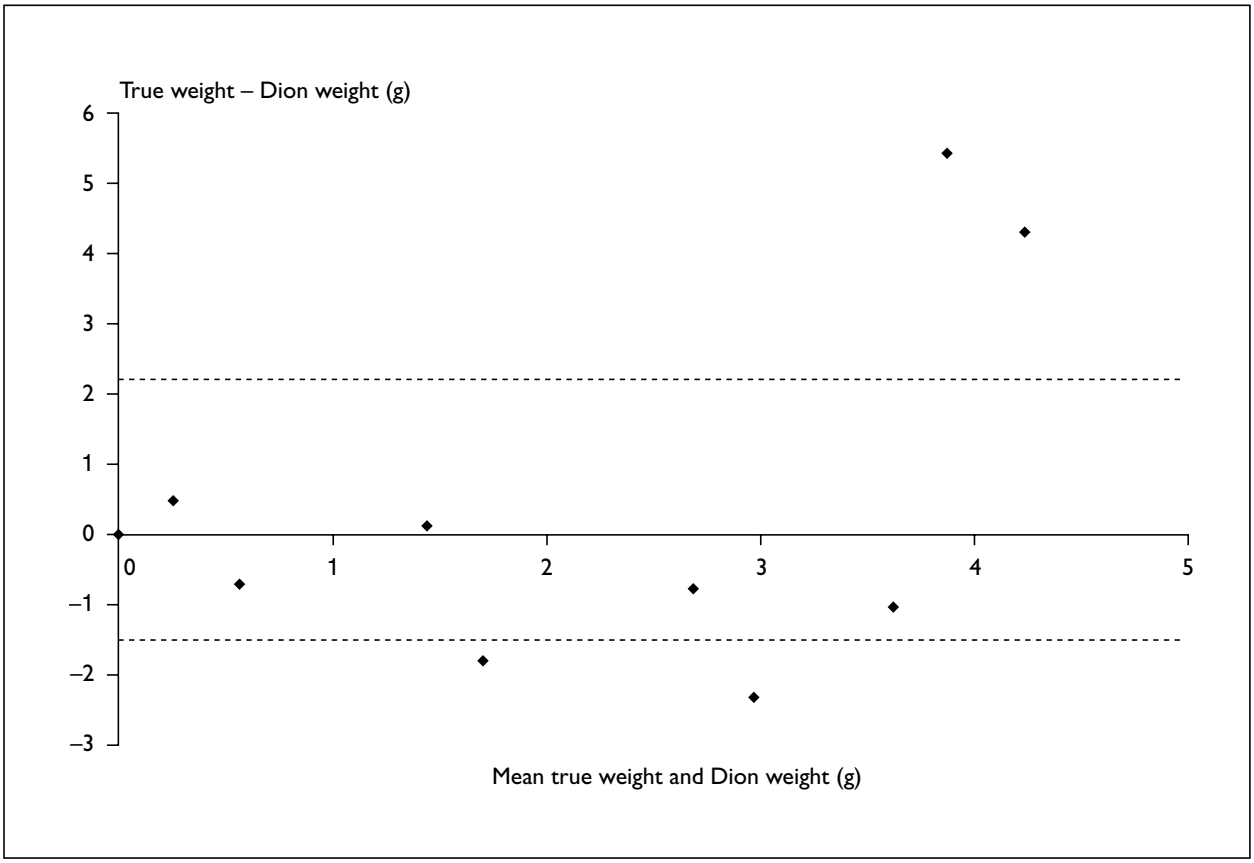


FIGURE 28 *The difference against the mean for the quantity of isoflurane used in the anaesthetic room*

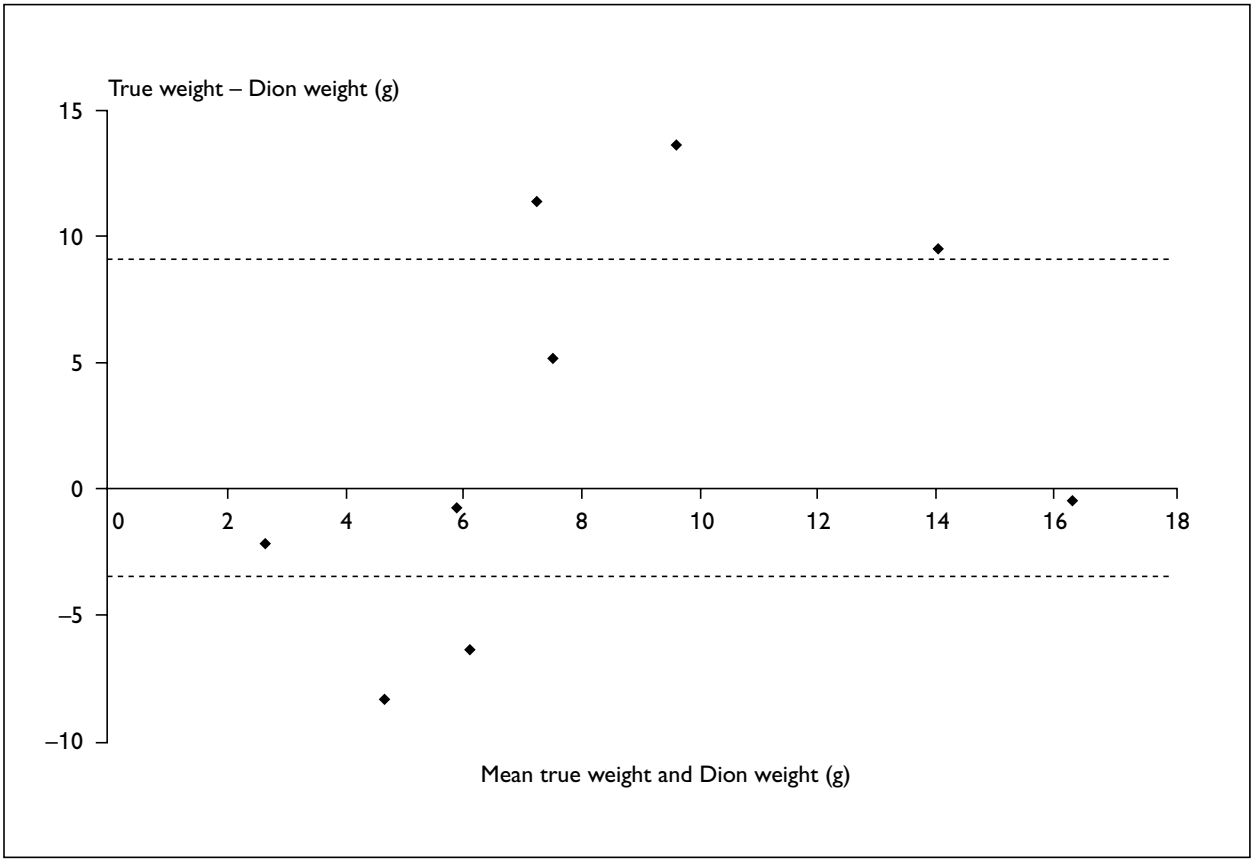


FIGURE 29 *The difference against the mean for the quantity of isoflurane used in the operating theatre*

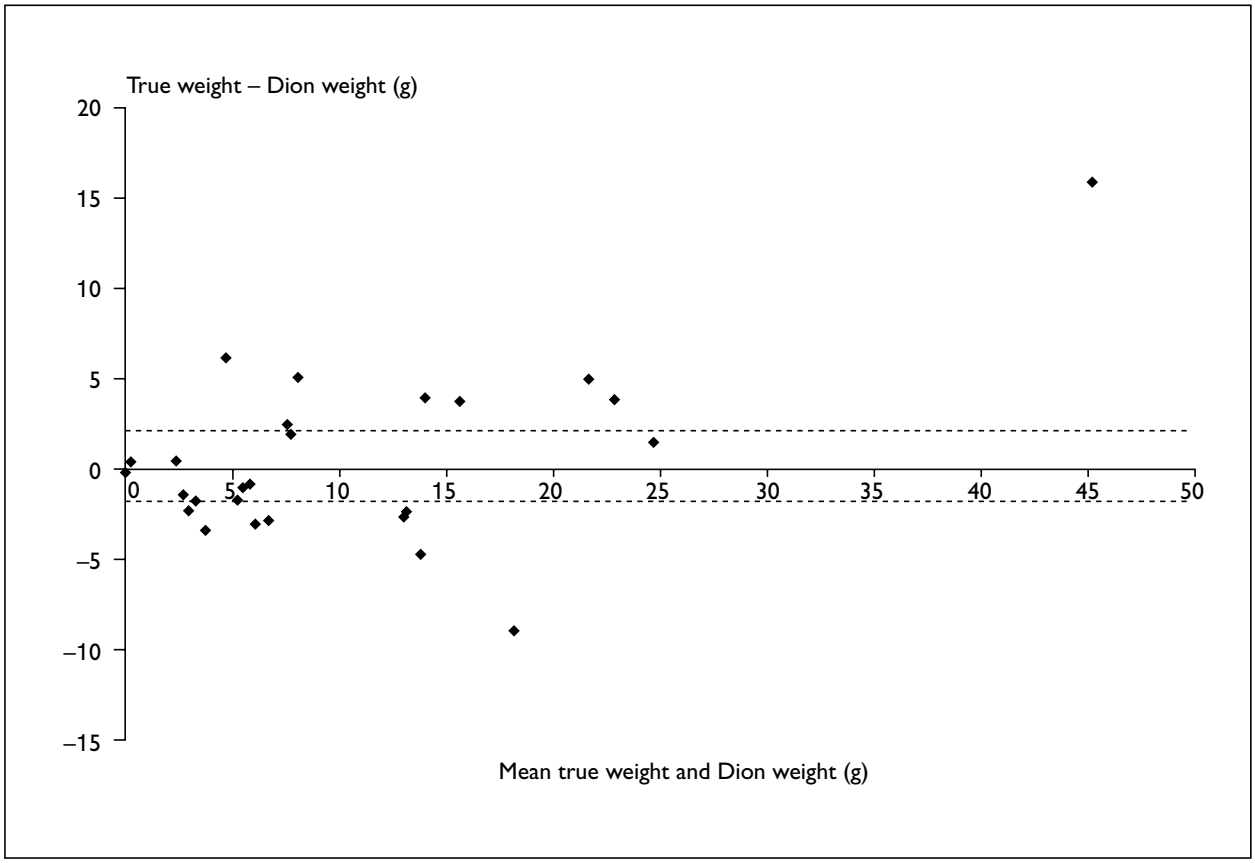


FIGURE 30 *The difference against the mean for the quantity of sevoflurane used in the anaesthetic room*

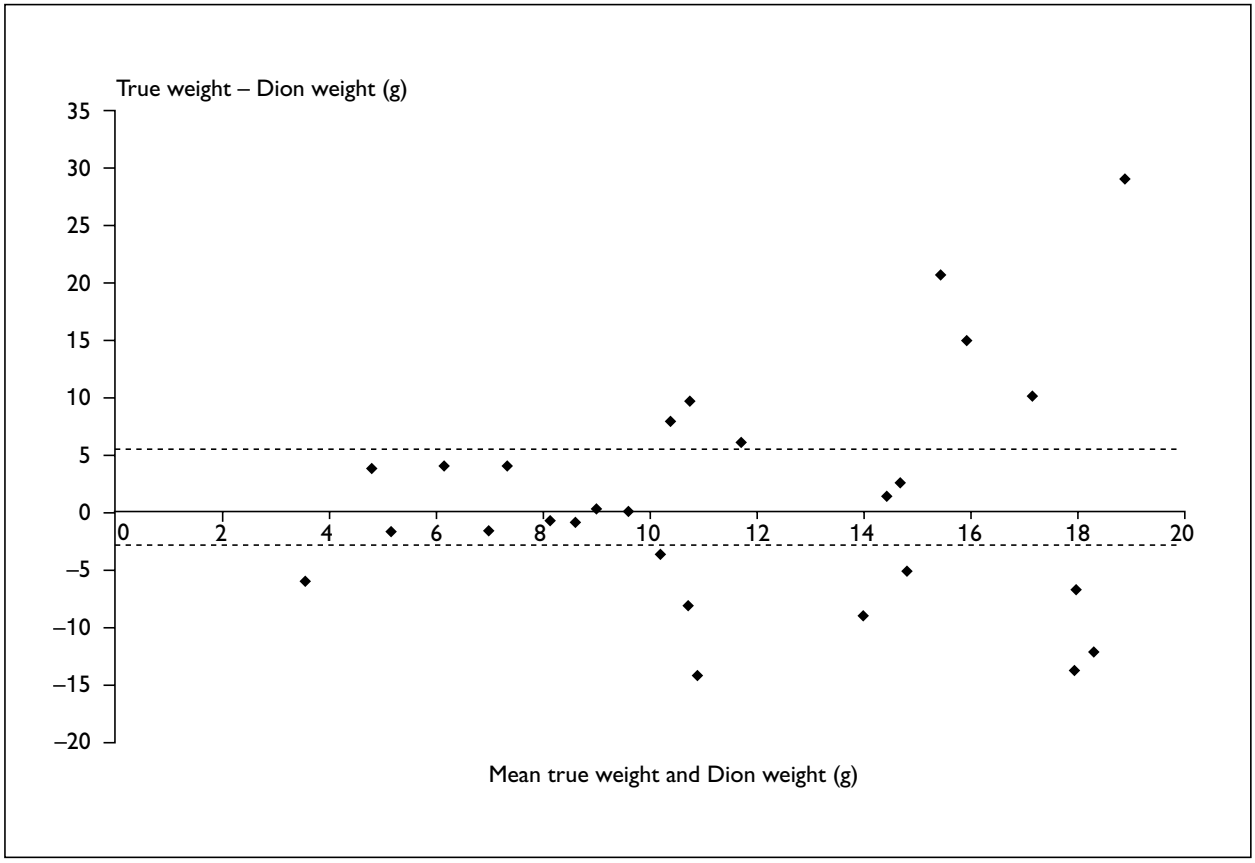


FIGURE 31 *The difference against the mean for the quantity of sevoflurane used in the operating theatre*

TABLE 89 *Limits of agreement for the weights of isoflurane and sevoflurane*

Volatile anaesthetic and area	Limits of agreement (g)
Isoflurane, anaesthetic room	–1.4 to 2.2
Isoflurane, theatre	–3.2 to 8.1
Sevoflurane, anaesthetic room	–1.2 to 2.5
Sevoflurane, theatre	–2.1 to 5.7

TABLE 90 *Correction factor for the Dion estimate of the quantity of volatile anaesthetic used*

Volatile anaesthetic and area	Mean true weight (g)	Mean Dion estimate (g)	Mean difference (true weight – Dion estimate) (g)	Correction factor (mean difference/ mean true weight x 100) (%)
Isoflurane, anaesthetic room	2.3	1.9	0.4	16
Isoflurane, theatre	9.1	6.7	2.0	27
Sevoflurane, anaesthetic room	11.1	10.5	0.6	6
Sevoflurane, theatre	12.6	10.8	1.8	14

TABLE 91 *Time over which volatile anaesthetic was given to the patients*

Volatile anaesthetic	Mean time administered (minutes)	95% CI (*n*)
Isoflurane, anaesthetic room	2.8	1.9 to 3.7 (10)
Sevoflurane, anaesthetic room	4.5	3.4 to 5.6 (29)
Isoflurane, operating theatre	21.6	7.5 to 35.7 (10)
Sevoflurane, operating theatre	20.6	11.8 to 26.3 (28)

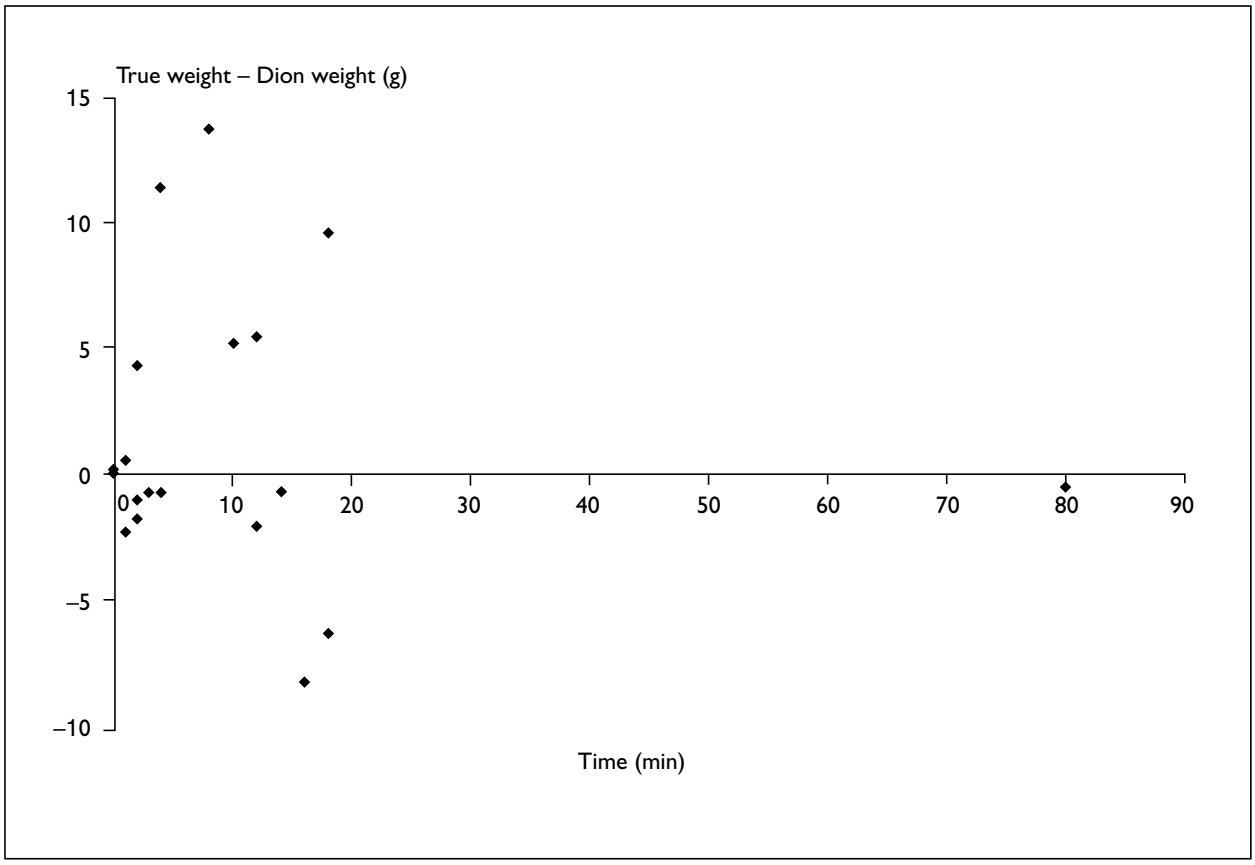


FIGURE 32 *The difference between the true weight and the estimated weight over time for isoflurane*

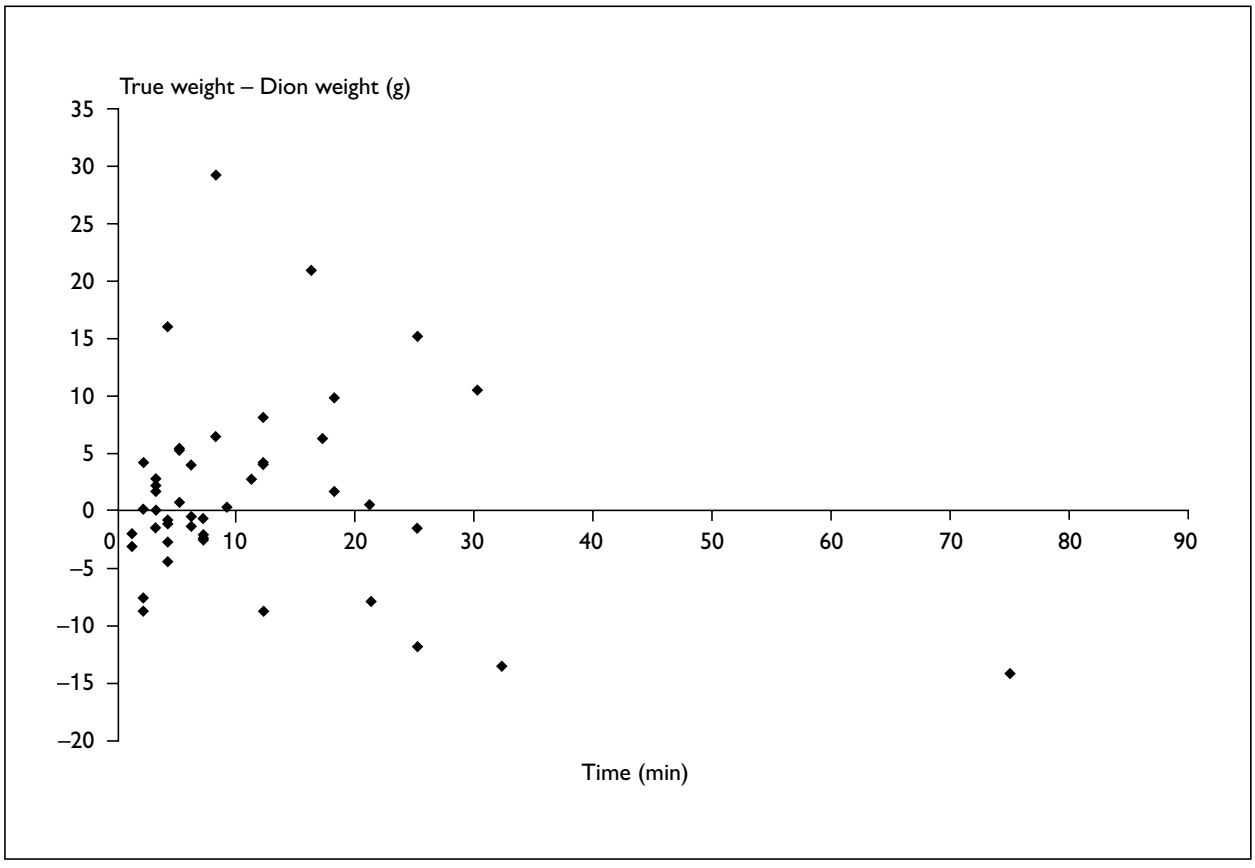


FIGURE 33 *The difference between the true weight and the estimated weight over time for sevoflurane*

Appendix 19

Calculating semi-fixed costs

Background

Semi-fixed costs account for resource use that remains unchanged over a range of output, but given sufficient changes in activity the costs increase or decrease. Staff costs are the principal component of semi-fixed costs for healthcare interventions. There was no available information on the resource use associated with the staff involved during the day procedure, but the type of surgical intervention and NHS trust study site was assumed to have an impact on the number and skill mix of the staff involved. There was no evidence to suggest that there would be differences in semi-fixed costs between the surgical groups or study sites included in the main study. A substudy was required to provide information on day-procedure staff deployment and skill mix to calculate the associated resource use and semi-fixed costs for each surgical group and study site. This substudy is referred to hereafter as the staff resource use study.

The aim of the staff resource use study was to provide information on staff deployment and skill mix during the day-surgery episode for each surgical group and study site included in the main study.

The objectives of the staff resource use study were to:

- confirm the stages and tasks that comprise a day-surgery episode
- identify the type and grade of NHS staff present at each stage of the day-surgery episode
- quantify the length of time each grade of NHS staff takes to complete each task during the stages of a day-surgery episode for the surgical groups and study sites included in the main study.

Method

Structured face-to-face interviews with NHS staff were used to confirm the tasks that a day-surgery episode comprises. Direct non-participant observation was selected as the preferred method to determine staff resource use. Subjective evaluation, self-reporting and collecting productivity data were alternative methods, but these do not have the advantage of being able to carefully describe and record the work of the person under observation[248] and may be subject to the potential bias of subjective, inexact or inaccurate recording.[249] Non-participant observation was used to collect data on staff resource use in the anaesthetic room and operating theatre. It was costly and impractical to observe directly the entire day-surgery episode and face-to-face interviews were used to collect NHS staff members' subjective estimates of resource use associated with the process of admitting and discharging, transferring between the theatre and the ward and monitoring postoperatively in recovery and on the ward.

The perspective of the staff resource use study was consistent with that of the empirical study and included costs accruing to the NHS staff resources. The staff resource use study started when the patient arrived at the hospital ward for their planned admission and ended when the patient was discharged from the care of the relevant NHS trust and left the hospital ward. Staff resource use at the preoperative clinic was excluded.

The type of NHS staff (e.g. surgeon, nurse), grade of NHS staff (e.g. consultant, grade E) and time spent working in the anaesthetic room and operating theatre were noted for each patient included in the staff resource use study sample. The unit costs (average salary per minute, including employer's contributions) for the relevant type and grade of NHS staff (see appendix 20) were then multiplied by their working time to calculate the total semi-fixed cost for each patient. The time spent in the anaesthetic room and operating theatre was recorded as part of the main study.

Study population

The target study population was composed of those patients who had been admitted to a ward, or unit, for day surgery in the main study NHS trust sites. The surgical groups matched those in the main study:

- patients aged over 18 years undergoing general, orthopaedic or gynaecological day surgery (adults)
- patients aged between 3 and 12 years undergoing general or ENT day surgery (paediatrics).

Study sample

The staff resource use study sample included all patients recruited into the main study in October and November 2000.

Analysis

An Excel 97® spreadsheet was used to record and analyse the data. Descriptive statistics (mean and 95% CIs) were calculated for the semi-fixed costs associated with each surgical group and study site.

Results

The stages of the day-surgery episode were confirmed during patient recruitment for the main study and four face-to-face interviews with nursing staff who cared for day patients at the NHS trust study sites (*Figure 34*). Four interviews with nursing staff from each hospital ward who cared for recruited patients determined the grade of staff and time taken to complete the component tasks of a day-surgery episode, excluding the anaesthetic room and operating theatre. The grade of staff and time to complete tasks was consistent between the study sites, but varied between adult and paediatric patients. The average semi-fixed cost per minute for the component tasks of the day-surgery episode was calculated for adult and paediatric patients (*Table 92*). The most notable difference between adult and paediatric levels of care for a day-surgery episode occurred during postoperative monitoring on the ward. Paediatric patients had dedicated care from one nurse for 2 hours, but one nurse would be expected to care for more than one adult patient.

One-hundred and ninety-four day procedures for recruited patients were directly observed in the anaesthetic room and operating theatre of the main study NHS trust sites. Differences in working practices in terms of skill mix were observed between the three hospital sites, but this did not translate into notable differences (the 95% CIs overlap) in the average semi-fixed costs. There was a detectable difference between the average semi-fixed costs of providing care in the anaesthetic room and operating theatre for adult and paediatric day surgery (*Table 93*).

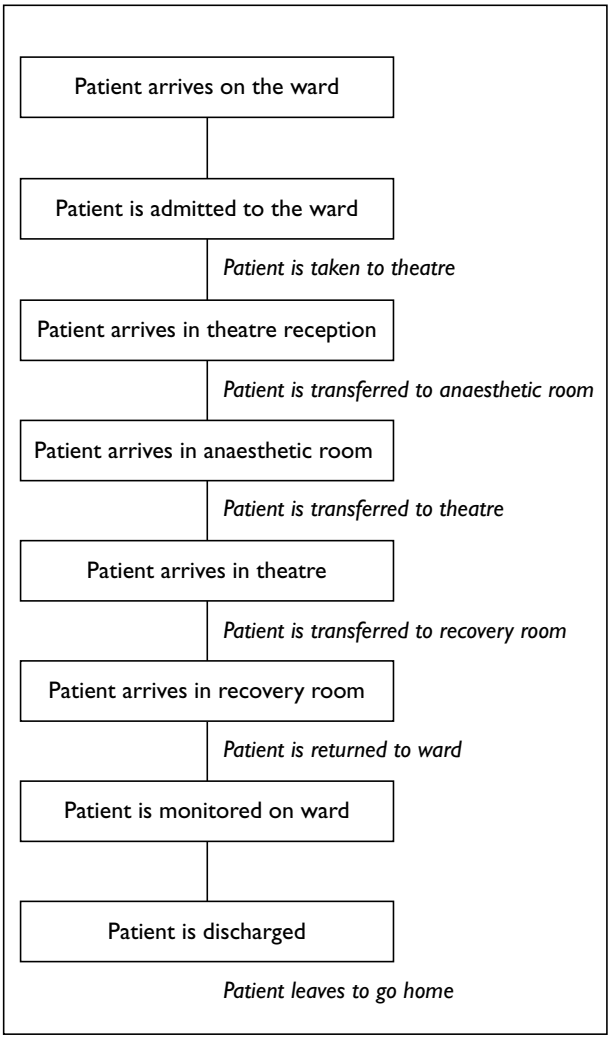


FIGURE 34 *The stages of the day-surgery episode*

Implications for the main study

This staff resource use study detected differences in the semi-fixed costs per minute for adult and paediatric practice. These semi-fixed costs per minute for each stage of the day-surgery episode were used to calculate the total cost in each arm of the adult and paediatric study, respectively.

TABLE 92 *Average semi-fixed costs per minute for a day-surgery episode, excluding anaesthetic room and operating theatre costs*

Task	Staff and grade	Time (min)	Average (95% CI) cost per minute (£)
Admitting patient to ward	Nurse grades D and E	Adult: 10 Child: 15	Adult: 1.73 (1.20 to 2.26) Child: 3.15 (NA)*
Transferring patient to theatre	Nurse grades D and E	Adult: 4 Child: 2	Adult: 0.66 (0.36 to 0.96) Child: 0.42 (NA)
Transferring patient from theatre	Nurse grades D and E	Adult: 4 Child: 2	Adult: 0.66 (0.36 to 0.96) Child: 0.42 (NA)
Monitoring patient in recovery	Nurse grades D and E	Adult: 20 Child: 20	Adult: 4.73 (4.04 to 5.42) Child: 3.80 (NA)
Monitoring patient on ward postoperatively	Nurse grades D and E	Adult: 5 Child: 120	Adult: 0.86 (0.56 to 1.16) Child: 25.20 (NA)
Discharging patient from ward	Nurse grades D and E	Adult: 10 Child: 10	Adult: 1.58 (1.05 to 2.11) Child: 2.10 (NA)

* *NA because* n = *1*

TABLE 93 *Average semi-fixed costs per minute for the anaesthetic room and operating theatre*

Area	Average semi-fixed cost per minute (95% CI; *n*) (£)
Anaesthetic room	Adult: 0.91 (0.86 to 0.96; 157) Child: 1.42 (1.15 to 1.69; 37)
Operating theatre	Adult: 2.15 (1.99 to 2.31; 157) Child: 2.07 (1.78 to 2.36; 37)

Appendix 20

NHS staff unit costs

All staff unit costs were for the year 2000 and the average salary excluding an 'out of hours' element for each grade of NHS staff was used (*Table 94*). The average salary per minute was calculated by assuming that doctors work 40 hours per week for 41 weeks a year (98,400 minutes) and nurses or theatre staff work 37.5 hours per week for 42 weeks a year (94,500 minutes).

The hours worked per year were taken from a published literature source.[244] A unit cost of zero was assumed for porters because the cost of their salary is included in the fixed cost attributed to each department in the NHS trust. Students are not paid by the NHS trust, and so a unit cost of zero was assumed in accordance with the study perspective.

TABLE 94 *Unit costs for NHS staff*

Type of staff	Grade of staff[250,251] *	Average salary excluding employer's contributions (£)	Employer's contributions (%)	Average salary including employer's contributions (£)	Average salary including employer's contributions (£/min)
Anaesthetist	Associate specialist	39,715	13.0	44,878	0.46
Anaesthetist	Consultant	56,273	17.2	65,951	0.67
Anaesthetist	Registrar	26,635	13.0	30,098	0.31
Anaesthetist	Senior registrar	31,405	13.0	35,488	0.36
Anaesthetist	Senior house officer	25,148	13.0	28,417	0.29
Anaesthetist	Specialist registrar	29,575	13.0	33,420	0.34
Anaesthetist	Staff grade	34,710	13.0	39,222	0.40
Anaesthetic/ theatre nurse, sister	Grade G	22,460	12.3	25,223	0.27
Auxiliary nurse, ODA, ODP	Grade A	10,005	12.3	11,236	0.12
Auxiliary/theatre nurse, HCA, ODA	HCA	10,005	12.3	11,236	0.12
Clinical nurse manager	Clinical nurse manager	24,859	12.3	27,916	0.30
Enrolled/staff/ theatre nurse	Grade D	15,668	12.3	17,595	0.19
Enrolled/theatre nurse, ODA, ODP	TP	16,458	12.3	18,482	0.20
HCA	Trainee HCA	8,000	12.3	8,984	0.10
Medical, midwife, nurse student	Student	0	–	0	0.00
Nurse	First assistant	23,531	12.3	26,425	0.28
ODA	ODA	15,831	12.3	17,778	0.19
ODA, ODP, staff nurse	SODA	19,911	12.3	22,359	0.24
Porter	Porter	0	–	0	0.00
Porter	Trainee porter	0	–	0	0.00

continued

***TABLE 94* contd** *Unit costs for NHS staff*

Type of staff	Grade of staff[250,251] *	Average salary excluding employer's contributions (£)	Employer's contributions (%)	Average salary including employer's contributions (£)	Average salary including employer's contributions (£/min)
Registered general nurse	Surgical assistant	23,531	12.3	26,425	0.28
SODA	MTO 3	19,911	12.3	22,359	0.24
Senior TP	Senior TP	18,541	12.3	20,822	0.22
Sister	Coordinator	23,598	12.3	26,501	0.28
Staff/scrub/ theatre nurse	Grade E	17,570	12.3	19,731	0.21
Staff/theatre nurse, sister	Grade F	19,645	12.3	22,061	0.23
Staff/theatre nurse, TP, ODA, ODP	Advanced TP	20,040	12.3	22,505	0.24
Surgeon	Associate specialist	39,715	13.0	44,878	0.46
Surgeon	Consultant	56,273	17.2	65,951	0.67
Surgeon	House officer	18,370	13.0	20,758	0.21
Surgeon	Registrar	26,635	13.0	30,098	0.31
Surgeon	Senior house officer	25,148	13.0	28,417	0.29
Surgeon	Specialist registrar	29,575	13.0	33,420	0.34
Surgeon	Staff grade	34,710	13.0	39,222	0.40
Theatre nurse	Bank nurse	15,668	12.3	17,595	0.19

* *Personal communication. Wirral: Wirral NHS Trust, 2000*

HCA, healthcare assistant; MTO 3, medical technical officer level 3; ODA, operating department assistant; ODP, operating department practitioner; SODA, senior operating department assistant; TP, theatre practitioner

Appendix 21

Calculating fixed costs

Background

Fixed costs account for resource use that remains unchanged with respect to output. The principal components of fixed costs associated with a day-surgery episode are capital and overhead costs associated with the use of hospital facilities, such as ward and operating theatre maintenance. The empirical study required information on the fixed costs associated with a day-surgery episode.

Method

A member of the relevant finance department from each of the NHS trusts was approached for information on the components and allocation of the day-surgery fixed costs for the ward, anaesthetic room and operating theatre. The costs related to the financial year 1999–2000.

The fixed cost per day patient was identified for three sections of the day-surgery episode: ward, anaesthetic room and operating theatre. Data available related to the average costs per episode. These were then used to estimate the fixed cost per hour related to a day-case episode, using the mean length of time spent in each section. The mean length of time spent in each section (ward, anaesthetic room, operating theatre) for a day-surgery episode was calculated from the results of the empirical study.

Results

One of the two finance departments was able to supply information on fixed costs in the necessary format. The components of the fixed costs were classified by the finance department as direct costs (e.g. staff and equipment) and indirect or overhead costs (e.g. domestic services and estates and energy). Staff costs were accounted for in the calculation of semi-fixed costs. To avoid double counting, the staff costs were subtracted from the total figure for fixed costs.

Fixed costs for the ward were derived to be £7.20 per patient/h and £1.80 per patient/h for the anaesthetic room and theatres.

Implications for the empirical study

The fixed costs per minute for the three sections of hospital facilities were used to calculate the total cost in each arm of the adult and paediatric studies.

Appendix 22

Quality control procedures

Quality assurance is defined as "all those actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with the guidelines for Good Clinical Practice (GCP) and the applicable regulatory requirements".[252]

Quality control is defined as "the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled".[252]

The following quality control procedures were used for the main study to ensure high standards of data collection, and procedures were followed throughout the duration of the study.

Adherence to study protocol

The two research nurses (GL and JB) monitored the recruited anaesthetists' adherence to the study protocol throughout the empirical study. All protocol violations were discussed with the lead investigator and classified as minor or major. Patients remained in the study if a minor protocol violation occurred, such as the fresh gas flow remaining above 4 l/min after 10 minutes for the propofol/propofol arm of the study. If a major protocol violation occurred, such as the patient being given a prophylactic anti-emetic or morphine, the patient was withdrawn from the study. There were a total of 12 major protocol violations in the paediatric study and 15 major protocol violations in the adult study.

Adherence to the study protocol was further validated by an external quality control procedure when the project coordinator (KP) accompanied the research nurses for 14 theatre lists. Three minor protocol violations were observed during these theatre lists. On two occasions the fresh gas flow rate exceeded 4 l/min for two patients randomised to receive propofol/propofol. One patient randomised to sevoflurane/sevoflurane was given 40 mg of propofol in theatre because they were not sufficiently anaesthetised. The patient was not withdrawn from the study, but this was recorded as a resource use. One major protocol violation was observed and the patient was withdrawn from the study because they were given morphine in theatre.

Identification and recruitment of suitable patients

The research nurses provided the principal investigator with a weekly record of patient recruitment. The weekly report contained:

- the number of eligible patients identified
- the number of eligible patients approached
- the number of patients recruited
- the number of patients who refused to participate
- the reasons why patients refused to participate
- the number of patients withdrawn after randomisation
- the reasons why patients withdrew after randomisation.

The project coordinator accompanied the research nurses on two occasions (Tuesday 7 March 2000 and Tuesday 4 April 2000) during the data-collection period to ensure patients were recruited and consented in a standardised way. Each research nurse used their own style to talk to potential study participants, but the same information was conveyed and patients were allowed time to decide whether they wished to take part. The research nurses explained the study to potential participants or their parents very clearly and in a consistent manner.

All consent forms were checked for completeness and collated and stored in The School of Pharmacy and Pharmaceutical Sciences, The University of Manchester.

Collecting and recording data

To ensure data were recorded in a consistent manner the project coordinator and each research nurse recorded simultaneously the perioperative resource use, patient characteristics and anaesthetic history data on four occasions (Tuesday 7

March, Tuesday 15 August, Tuesday 4 April and Tuesday 15 August 2000) during the data collection. The project coordinator entered the simultaneously recorded data on patients recruited by the research nurses onto the Access® database. The data entries were then checked for consistency.

Two methods were used to monitor data collection from the telephone interviews. The project coordinator observed the two research nurses doing two telephone interviews. The system for conducting the telephone interviews was changed in April 2000 and two registered nurses (CW and JT) were recruited as telephone interviewers. Both telephone interviewers were given information on a 'mock' patient on whom they conducted a 'mock' telephone interview. The project coordinator played the role of the 'mock' patient in June 2000, but the telephone interviewers were not aware of the identity of the 'mock' patient at the time of the telephone interview. Both telephone interviewers consented to take part in this quality control procedure. The telephone interviewers were professional and clear in their approach and no differences in telephone interview technique were observed.

Data entry

The data were recorded by hand in structured data-entry booklets and then entered into an Access® database. Ensuring completeness of the perioperative resource use, patient characteristics and anaesthetic history data was dealt with at the design stage of the Access® database, which had drop-down menus and defaults set to ensure that predefined basic information was entered. In addition, all data collected were checked for completeness by the principal investigator and the project coordinator. Where possible, missing data were identified and found from patients' medical records.

Appendix 23

Reasons for refusing to participate in and for withdrawal from the empirical study

TABLE 95 *Reasons for refusal to participate in the empirical study*

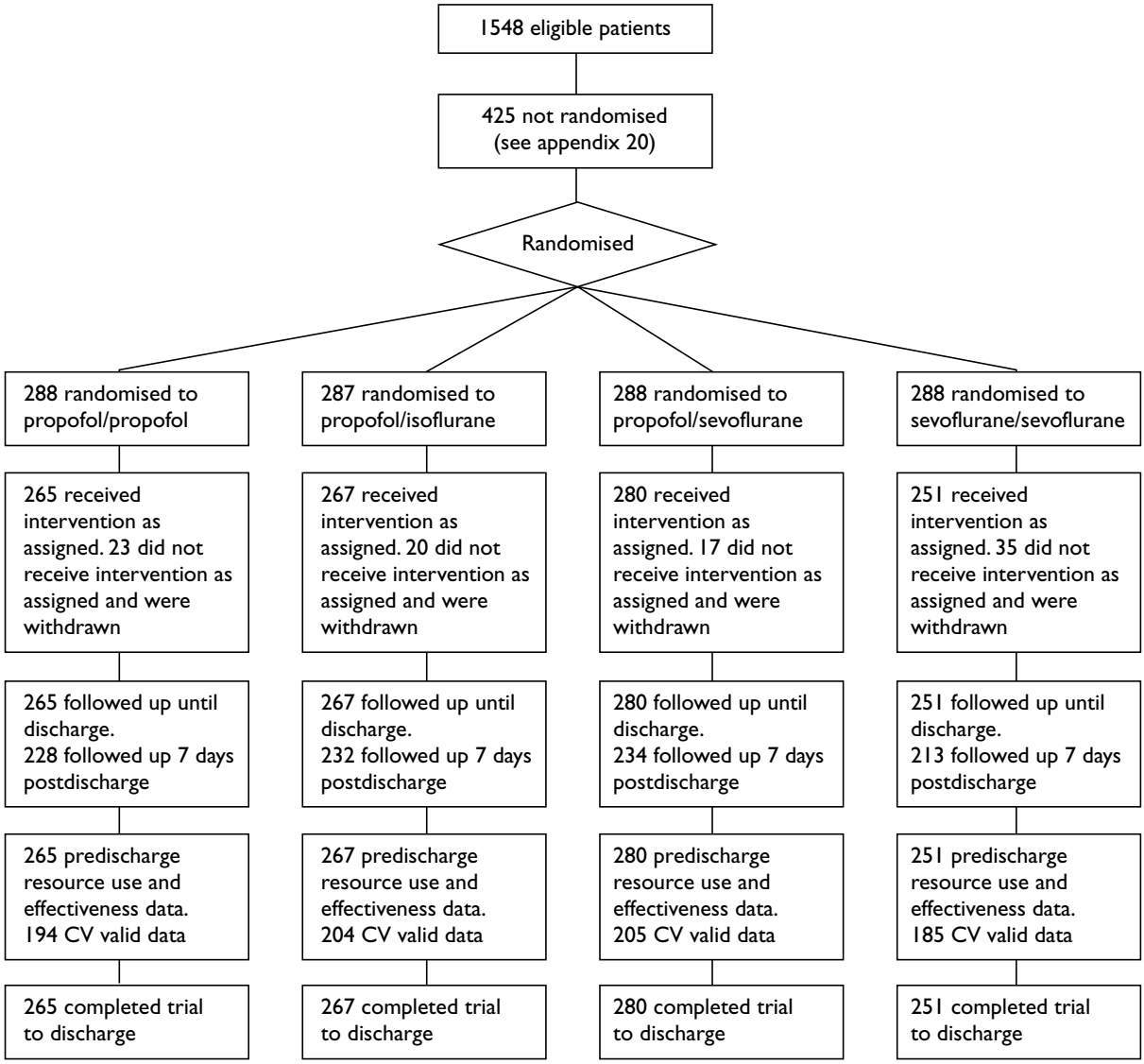
Reason	No. of patients	
	Children	Adults
Do not want gas or mask	59	226
No time to take part	12	12
No reason given but do not want to take part	7	34
I want the anaesthetist to choose	7	17
Do not like idea of study	7	17
Do not want injection	6	5
Been in study before	5	8
Scared generally	4	37
Legal/ethical reasons	4	4
Want anaesthetic had before	3	10
Concurrent disease and worried about the effect	3	5
Not enough time to think about taking part	1	20
Do not know	0	18
Previous bad experience/nausea with anaesthetic	0	9
Previously aware during anaesthesia	0	2
Do not want researcher to see medical records	0	1
Total	118	425

TABLE 96 *Reasons for withdrawal from the empirical study*

Reason	No. of patients	
	Children	Adults
Study protocol violations	12	15
Operation cancelled due to unsuitable patient	3	11
Operation cancelled due to insufficient time	2	9
Patient withdrew consent, did not want gas	2	7
Patient withdrew consent, no reason given	2	5
Patient did not fulfil inclusion criteria	1	11
Anaesthetist not content with randomised technique	1	6
Comorbidity meant unsuitable randomisation	1	5
Patient withdrew consent, did not want injection	1	2
Researcher not able to be in two places	0	9
Anaesthetist not happy to take part	0	5
Do not know	0	4
Theatre not equipped for anaesthetic technique	0	3
Complications with surgery	0	2
Previous complications with anaesthesia	0	1
Total	25	95

Appendix 24

Profile of the adult trial



Appendix 25

Surgical procedure coding and summarised groups

Patients were coded using the OPCS Classification of Surgical Operations and Procedures.[261] There were 217 coded procedure types. For ease of presentation, these were summarised into the categories listed below.

Ear – minor

D01.3 excision of preauricular abnormality
D02.1 excision of lesion of external ear
D07.2 removal of wax from exterior auditory canal
D07.3 removal of foreign body in exterior auditory canal
D15.1 insertion of vent tube through tympanic membrane
D15.2 suction clearance of middle ear
D15.3 incision of ear drum
D19.8 other specified extirpation of lesion of middle ear
D19.9 unspecified extirpation of lesion of middle ear
D20.1 biopsy of lesion of middle ear
D20.2 maintenance of vent tube through tympanic membrane
D20.3 removal of vent tube from tympanic membrane
D28.2 examination of ear under anaesthetic
D28.9 unspecified ear operation.

Nose – minor

E02.9 plastic operations on nose (unspecified)
E02 plastic operations on nose
E04.1 submucous diathermy to turbinate of nose
E04.6 cauterisation of turbinate of nose
E05.1 cauterisation of internal nose
E08.5 removal of foreign body from cavity of nose
E09.8 other specified external nose operation
E09.9 operations on external nose
E10.9 unspecified nose operation
E12.3 irrigation of maxillary antrum using sublabial approach.

Throat – minor

E36.9 diagnostic endoscopic examination of larynx.

Throat – intermediate

E20.1 total adenoidectomy.

Dental – minor

F10.9 simple extraction of tooth
F13.5 restoration of part of tooth.

Gastrointestinal tract – minor

H22.9 unspecified diagnostic endoscopic examination of colon
H25.9 unspecified diagnostic endoscopic examination of lower bowel (f/s)
H25 diagnostic endoscopic examination of lower bowel (f/s)/*fibreoptic sigmoidoscope.

Gastrointestinal tract – intermediate

G23 repair of diaphragmatic hernia

T19.1 bilateral herniotomy
T19.3 ligation of patent processus vaginalis
T19.8 simple excision of inguinal hernia sac
T20 primary repair of inguinal hernia
T21.2 repair of recurrent inguinal hernia using insertion of prosthetic material
T22 primary repair of femoral hernia
T24 repair of umbilical hernia
T24.3 repair of umbilical hernia using sutures
T29.8 unspecified operation on umbilicus
T31.8 other operations on anterior abdominal wall (other specified).

Peritoneum

T34.9 open drainage of peritoneum
T43.9 diagnostic endoscopic examination of peritoneum

H51.1 haemorrhoidectomy
H52.4 rubber band ligation of haemorrhoid
H55.9 other operations on perianal region
H56.4 excision of anal fissure.

Peripheral (legs)

L85 ligation of varicose vein of leg
L85.1 ligation of long saphenous vein
L85.2 ligation of short saphenous vein
L87.4 avulsion of varicose vein of leg
L87 other operations on varicose vein of leg.

Urology

M29.2 endoscopic insertion of tubal prosthesis in ureter
M30 diagnostic endoscopic examination of ureter
M30.1 endoscopic retrograde pyelography
M30.9 diagnostic endoscopic examination of ureter
M42.1 endoscopic resection of lesion of bladder
M42.2 endoscopic cauterisation of lesion of bladder
M45.1 diagnostic endoscopic examination of bladder and biopsy of lesion
M45.9 unspecified diagnostic endoscopic examination of bladder
M45 diagnostic endoscopic examination of bladder
M47.2 change of urethral catheter into bladder
M56.3 endoscopic injection of outlet of female bladder
M58.2 dilatation of outlet of female bladder
M76.4 endoscopic dilatation of urethra
M79.2 dilatation of urethra not elsewhere classified (NEC).

Scrotum/testes

M81.3 external meatotomy of urethral orifice

N01.2 excision of lesion of scrotum
N03.9 other operations on scrotum
N08.2 one stage bilateral orchidopexy NEC
N08 bilateral placement of testis in scrotum
N09.2 one stage orchidopexy NEC
N09.9 other placement of testis in scrotum, unspecified
N09 other placement of testis in scrotum
N11.1 excision of hydrocele
N11 operations on hydrocele sac
N13.2 fixation of testis
N13.3 reduction of torsion of testis
N15.3 excision of lesion of epididymis.

Penis

N17.1 bilateral vasectomy
N17 excision of vas deferens
N20.4 vasotomy
N27.1 excision of lesion of penis
N28.4 frenuloplasty of penis
N28.5 frenuloplasty of penis
N28 plastic operations on penis
N30.1 prepuceplasty
N30.2 freeing of adhesions of prepuce
N30.3 circumcision
N32.1 excision of lesion of penis.

Vulva/vagina

P03.1 excision of Bartholin gland
P03.2 marsupialisation of Bartholin gland
P05.4 excision of lesion of vulva NEC
P05.5 excision of excess labial tissue
P05.8 excision of vulva, other specified
P06.3 cauterisation of lesion of vulva
P07.1 plastic repair of vulva
P09.1 biopsy of lesion of vulva
P09.2 drainage of lesion of vulva
P09 other operations on vulva
P11.1 excision of lesion of female perineum
P11 extirpation of lesion of female perineum
P13.8 other operations on female perineum
P14.9 incision of introitus of vagina (unspecified)
P15.4 incision of vulva
P20.1 excision of lesion of vagina
P20.2 laser destruction of lesion of vagina
P20.3 cauterisation of lesion of vagina
P27 exploration of vagina
P29.5 dilatation of vagina.

Cervix

P27.3 colposcopy

Q02.1 wedge excision of cervix and suture of, however further qualified
Q02.3 cauterisation of lesion of cervix
Q03.3 cone biopsy of cervix

Q03.4 punch biopsy of cervix
Q03.5 ring biopsy of cervix
Q03 biopsy of cervix
Q55.3 Papinacolau smear.

Other gynaecology – minor

Q05 other operations on uterus and cervix
Q05.1 repair of cervix or uterus
Q05.2 dilatation of cervix
Q10.1 dilatation of cervix and curettage of products of conception
Q10.2 curettage of products of conception
Q10.3 dilatation and curettage
Q11.2 dilatation of cervix and evacuation of products of conception
Q12.1 introduction of intrauterine device (IUD)
Q12.2 replacement of IUD
Q12.3 removal of displaced IUD
Q12.4 removal of IUD
Q12 IUD
Q17.1 endoscopic resection of uterus lesion
Q17.2 endoscopic cauterisation of uterus lesion
Q18 diagnostic endoscopic examination of uterus
Q18.1 diagnostic endoscopic examination and biopsy of uterus
Q18.8 diagnostic endoscopic examination and biopsy of uterus, other
Q18.9 diagnostic endoscopic examination and biopsy of uterus, unspecified
Q55.1 examination under anaesthetic of female genital tract and Papinacolau smear
Q55.2 examination of female genital tract under anaesthetic NEC.

Other gynaecology – intermediate

Q22.3 bilateral oophorectomy
Q23 unilateral excision of adnexa of uterus
Q25.1 excision of lesion of Fallopian tube
Q27.2 open bilateral clip of Fallopian tubes
Q35 endoscopic bilateral occlusion of Fallopian tube
Q35.2 endoscopic bilateral clip of Fallopian tube
Q38 other therapeutic endoscopic operation of Fallopian tube
Q38.1 endoscopic freeing of adhesions of Fallopian tube
Q39 diagnostic endoscopic examination of Fallopian tube
Q39.1 diagnostic endoscopic examination of Fallopian tube and lesion biopsy
Q39.9 diagnostic endoscopic examination of Fallopian tubes
Q41.1 salpingography
Q41.3 dye test of Fallopian tube
Q41.5 operations to ensure patency of Fallopian tube
Q43.2 excision of lesion of ovary
Q49.2 endoscopic freeing of adhesions of ovary
Q49.3 endoscopic drainage of ovary cyst
Q49.8 therapeutic endoscopic operations on ovary
Q49 therapeutic endoscopic operations on ovary
Q52.2 destruction of lesion of broad ligament of uterus
Q54.1 suspension of uterus
Q8.1 vaginal hysterocolpectomy and excision of periuterine tissue
Q8.9 vaginal excision of uterus (unspecified).

Skin – minor

S02.9 unspecified plastic excision of skin of abdominal wall
S04.2 excision of sweat gland bearing skin, groin
S04.3 excision of sweat gland bearing skin, groin, NEC
S06.2 marsupialisation of lesion of skin, NEC
S08.3 curettage of lesion of skin of head or neck, NEC
S15.2 biopsy of lesion of skin, NEC
S23.2 z plasty, NEC
S45.3 removal of organic material of head or neck
S60.4 refashioning of scar, NEC
S68.1 total excision of nail
S70.1 avulsion of nail.

Tendons, muscles, soft tissue

T59.1 excision of ganglion of wrist
T59.2 excision of ganglion of hand, NEC
T60.1 excision of ganglion of wrist
T52.1 palmar fasciectomy
T54.1 division of palmar fascia
T54.9 division of fascia (unspecified)
T67.1 primary repair of tendon, tendon transfer
T67 primary repair of tendon
T69 freeing of tendon
T70.2 tenotomy, NEC
T70.5 lengthening of tendon
T81.3 biopsy lesion of muscle, NEC
T87.7 excision biopsy of inguinal lymph node
T87 excision or biopsy of lymph node
T96.1 excision of cystic hygroma
T96.2 excision of soft tissue NEC

V41.2 anterior attachment of correctional instrument to spine

A67.9 release of trapped peripheral nerve

B10.1 excision of thyroglossal cyst.

Bone

W03.5 localised fusion of joints of midfoot and forefoot
W28.3 removal of interior fixation from bone NEC
W32 other graft of bone

X11.2 amputation of phalanx of toe
X11 amputation of toe

Y42 manipulation of organ, NEC

Z89.1 shoulder, NEC.

Knee

W82.3 endoscopic repair of semilunar cartilage
W85.1 endoscopic removal of loose body from knee joint
W85.2 endoscopic irrigation of knee joint
W85 therapeutic endoscopic operations on knee joint cavity
W86.1 endoscopic removal of loose body from joint, NEC
W87.1 diagnostic endoscopic examination of knee joint and biopsy lesion
W87.9 diagnostic endoscopic examination of knee joint and biopsy lesion
W87 diagnostic endoscopic examination of knee joint.

Joints

W62.9 other primary fusion of other joint
W81.5 exploration of joint, NEC
W88.9 endoscopic examination of other joint, unspecified
W90.1 aspiration of joint
W90.3 injection of therapeutic substance into joint
W91 other manipulation of joint
W92.4 examination of joint under anaesthetic.

Breasts

B27.9 total excision of breast
B28 other excision of breast.

Appendix 26

Analysis of confounding factors for PONV in the adult study

This section displays the association between PONV and other variables, which plausibly might be associated with risk. Tables are displayed to check the evenness of the distributions of these potential confounding variables across the randomisation arms. The total numbers of subjects shown in the tables vary slightly, since some of the variables have missing data. Probability values presented with tables refer, unless otherwise stated, to a simple test for heterogeneity among categories. So-called 'exact' tests were employed when appropriate. Probability values are not presented for tables examining the distribution of potential confounding variables among the randomisation categories, as the statistical significance of observed differences is not relevant to the question of confounding.

Gender

Table 97 shows a marked gender difference in risk of PONV. The marked gender difference is also present, and in the same direction, when one or more episodes and two or more episodes of vomiting are examined (data not displayed). *Table 98* confirms that the difference in PONV among anaesthetic regimens is true for both genders, although varying around differing bases.

Age

Table 99 shows the age breakdown of the adult population in four nearly equally sized groups (quartiles). These quartiles are employed in a number of tabulations that follow. Even though the male and female age distributions differ, these same quartiles are, for simplicity of presentation, used when sex-specific tabulations are presented. This made no material difference to the interpretation of the data and age was used on its natural scale in the subsequent regression analyses. The age ranges of quartiles are:

1. < 32.4
2. 32.4–41.2
3. 41.3–53.4
4. > 53.4.

Table 99 shows a marked gradient in PONV by age; the older patients appear to be at less risk. This pattern is maintained when one or more episodes of vomiting is considered. However, *Table 100* demonstrates a strong gradient with age among women only, not among men. The pattern (and statistically significant gradient for women) remains when one or more episodes of vomiting is considered. The marked age difference is also present, and in the same pattern, when one or more episodes and two or more episodes of vomiting are examined. Tabulation of one or more episodes of vomiting shows a linear trend for women ($p < 0.01$).

Type of surgery

Tables 101 and *102* show that within broad categories of surgical procedure there are differences in risk, the high level in gynaecology is similar to the results of other trials. The data for women

TABLE 97 *Occurrence of any PONV by gender in the adult study*

	No. of patients		
	Men	**Women**	**Total**
Total	269 (100%)	792 (100%)	1061 (100%)
Nausea or vomiting – no	259 (96.3%)	595 (75.1%)	854 (80.5%)
Nausea or vomiting – yes	10 (3.7%)	197 (24.9%)	207 (19.5%)
p < *0.001*			

TABLE 98 *Occurrence of any PONV by randomisation group and gender in the adult study*

	No. of patients				
	Propofol/ propofol	**Propofol/ isoflurane**	**Propofol/ sevoflurane**	**Sevoflurane/ sevoflurane**	**Total**
Men					
Total	66 (100%)	72 (100%)	70 (100%)	61 (100%)	269 (100%)
Nausea or vomiting – no	65 (98.5%)	72 (100%)	68 (97.1%)	54 (88.5%)	259 (96.3%)
Nausea or vomiting – yes	1 (1.5%)	0 (0%)	2 (2.9%)	7 (11.5%)	10 (3.7%)
Women					
Total	201 (100%)	197 (100%)	207 (100%)	187 (100%)	792 (100%)
Nausea or vomiting – no	165 (82.1%)	148 (75.1%)	163 (78.7%)	119 (63.6%)	595 (75.1%)
Nausea or vomiting – yes	36 (17.9%)	49 (24.9%)	44 (21.3%)	68 (36.4%)	197 (24.9%)
χ^2: *men*, p < *0.004; women,* p < *0.001*					

TABLE 99 *Occurrence of PONV by age quartile in the adult study*

	No. of patients				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Total**
Total	264 (100%)	266 (100%)	266 (100%)	265 (100%)	1061 (100%)
Nausea or vomiting – no	180 (68.2%)	200 (75.2%)	225 (84.6%)	249 (94.0%)	854 (80.5%)
Nausea or vomiting – yes	84 (31.8%)	66 (24.8%)	41 (15.4%)	16 (6%)	207 (19.5%)

TABLE 100 *Occurrence of PONV by age quartile (total study population) and gender in the adult study*

	No. of patients				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Total**
Men					
Total	50 (100%)	53 (100%)	50 (100%)	116 (100%)	269 (100%)
Nausea or vomiting – no	46 (92.0%)	52 (98.1%)	47 (94.0%)	114 (98.3%)	259 (96.3%)
Nausea or vomiting – yes	4 (8.0%)	1 (1.9%)	3 (6.0%)	2 (1.7%)	10 (3.7%)
Women					
Total	214 (100%)	213 (100%)	216 (100%)	149 (100%)	792 (100%)
Nausea or vomiting – no	134 (62.6%)	148 (69.5%)	178 (82.4%)	135 (90.6%)	595 (75.1%)
Nausea or vomiting – yes	80 (37.4%)	65 (30.5%)	38 (17.6%)	14 (9.4%)	197 (24.9%)
χ^2: *men*, p > *0.1 (linear trend); women*, p > *0.001 (linear trend)*					

TABLE 101 *Occurrence of PONV by broad surgical procedure categories and gender in the adult study*

	No. of patients					
	Women, general	**Men, general**	**Women, gynaecology**	**Women, orthopaedic**	**Men, orthopaedic**	**Total**
Total	77 (100%)	184 (100%)	684 (100%)	31 (100%)	85 (100%)	1061 (100%)
Nausea or vomiting – no	65 (84.4%)	178 (96.7%)	506 (74.0%)	24 (77.4%)	81 (95.3%)	854 (80.5%)
Nausea or vomiting – yes	12 (15.6%)	6 (3.3%)	178 (26.0%)	7 (22.6%)	4 (4.7%)	207 (19.5%)
χ^2: p < *0.001*						

TABLE 102 *Occurrence of one or more episodes of vomiting by broad surgical procedure categories and gender in the adult study*

	No. of patients					
	Women, general	**Men, general**	**Women, gynaecology**	**Women, orthopaedic**	**Men, orthopaedic**	**Total**
Total	77 (100%)	184 (100%)	684 (100%)	31 (100%)	85 (100%)	1061 (100%)
One or more episodes of vomiting – no	72 (93.5%)	183 (99.5%)	640 (93.6%)	27 (87.1%)	84 (98.8%)	1006 (94.8%)
One or more episodes of vomiting – yes	5 (6.5%)	1 (0.5%)	44 (6.4%)	4 (12.9%)	1 (1.2%)	55 (5.2%)
χ^2: p < *0.001*						

given in *Table 103* confirm the age trends within general surgery and gynaecology. The number of women undergoing orthopaedic surgery was too small to characterise any trend, should one be present. The numbers in the various categories become too small to discern any clear pattern for two or more episodes of vomiting.

Recovery of awareness

Table 104 shows that patients deemed to be agitated on recovering awareness after anaesthesia were much more likely to suffer PONV (43%) than those who were alert (14%) or drowsy (25%). A similar pattern occurs when one or more episodes of vomiting is considered, but the heterogeneity is compatible with being a chance effect ($p > 0.5$).

ASA grade

Consideration of the ASA grade (*Table 105*) shows increased occurrence of PONV among patients in ASA grade 1. There is no discernible pattern when one or more episodes of vomiting is considered. For one or more episodes of vomiting there is no discernible pattern.

Previous anaesthetic experience

Patients reported a mean of 3.2 previous anaesthetic experiences (median, 2.0; SD, 3.8; range, 0–41). There was no difference between randomised groups. *Table 106* shows that the occurrence of PONV was not strongly enough associated with the number of previous anaesthetics received by the patients to yield a

TABLE 103 *Occurrence of PONV among women by surgical procedure and age quartile in the adult study*

	No. of patients				
	Quartile 1	**Quartile 12**	**Quartile 13**	**Quartile 14**	**Total**
General					
Total	16 (100%)	8 (100%)	19 (100%)	34 (100%)	77 (100%)
Nausea or vomiting – no	12 (75.0%)	6 (75.0%)	15 (78.9%)	32 (94.1%)	65 (84.4%)
Nausea or vomiting – yes	4 (25.0%)	2 (25.0%)	4 (21.1%)	2 (5.9%)	12 (15.6%)
Gynaecology					
Total	193 (100%)	197 (100%)	188 (100%)	106 (100%)	684 (100%)
Nausea or vomiting – no	117 (60.6%)	137 (69.5%)	155 (82.4%)	97 (91.5%)	506 (74.0%)
Nausea or vomiting – yes	76 (39.4%)	60 (30.5%)	33 (17.6%)	9 (8.5%)	178 (26.0%)
Orthopaedics					
Total	5 (100%)	8 (100%)	9 (100%)	9 (100%)	31 (100%)
Nausea or vomiting – no	5 (100%)	5 (62.5%)	8 (88.9%)	6 (66.7%)	24 (77.4%)
Nausea or vomiting – yes	0 (0%)	3 (37.5%)	1 (11.1%)	3 (33.3%)	7 (22.6%)
Tests for linear trend by age: general, p < *0.07; gynaecology*, p < *0.001; orthopaedics*, p > *0.6*					

TABLE 104 *Occurrence of PONV by awareness on recovery from anaesthetic in the adult study*

	No. of patients			
	Alert	**Agitated/ distressed**	**Drowsy**	**Total**
Total	618 (100%)	68 (100%)	367 (100%)	1053 (100%)
Nausea or vomiting – no	534 (86.4%)	39 (57.4%)	274 (74.7%)	847 (80.4%)
Nausea or vomiting – yes	84 (6.5%)	29 (42.6%)	93 (25.3%)	206 (19.6%)
χ^2: p < *0.001*				

TABLE 105 *Occurrence of PONV by ASA grade in the adult study*

	No. of patients				
	ASA category not known	**ASA category 1**	**ASA category 2**	**ASA category 3**	**Total**
Total	15 (100%)	720 (100%)	308 (100%)	11 (100%)	1054 (100%)
Nausea or vomiting – no	13 (86.7%)	560 (77.8%)	263 (85.4%)	11 (100%)	847 (80.4%)
Nausea or vomiting – yes	2 (13.3%)	160 (22.2%)	45 (14.6%)	0 (0%)	207 (19.6%)
χ^2: p < *0.02*					

TABLE 106 *Occurrence of PONV by tertile group of previous number of occasions on which anaesthesia received for the adult study*

	No. of patients			
	0 or 1 previous occasions	**2 or 3 previous occasions**	**4 or more previous occasions**	**Total**
Total	352 (100%)	389 (100%)	320 (100%)	1061 (100%)
Nausea or vomiting – no	275 (78.1%)	313 (80.5%)	266 (83.1%)	854 (80.5%)
Nausea or vomiting – yes	77 (21.9%)	76 (19.5%)	54 (16.9%)	207 (19.5%)
χ^2: p > *0.1 (linear trend)*				

statistically significant trend. Nevertheless, visually there is the suggestion that the risk of PONV declines with increasing anaesthetic experience. This observation was tested by including the actual number of previous anaesthetics, rather than a grouped variable, into a logistic regression (see chapter 5).

Duration of anaesthesia

Table 107 shows that the risk of PONV depends on the duration of anaesthesia. A similar pattern was found for one or more episodes of vomiting (linear trend, $p < 0.02$)

Anaesthetic regimen

Tables 108 and *109* display how some of the variables associated with the occurrence of PONV are distributed among the anaesthetic regimens; gender is not displayed, as random allocation was within single gender groups. Such differences as occur are small.

These data indicate that the marked increase in occurrence of PONV among patients receiving sevoflurane/sevoflurane may represent a real effect (i.e. the effect is due neither to chance nor confounding).

TABLE 107 *Occurrence of PONV by duration of anaesthesia in the adult study*

	No. of patients			
	Duration < 15 min	**Duration 15 to < 24 min**	**Duration > 24 min**	**Total**
Total	341 (100%)	356 (100%)	353 (100%)	1050 (100%)
Nausea or vomiting – no	310 (90.9%)	281 (78.9%)	256 (72.5%)	847 (80.7%)
Nausea or vomiting – yes	31 (9.1%)	75 (21.1%)	97 (27.5%)	203 (19.3%)
χ^2: p < *0.001 (linear trend)*				

TABLE 108 *Degree of orientation category by randomisation groups in the adult study*

	No. of patients				
	Propofol/ propofol	**Propofol/ isoflurane**	**Propofol/ sevoflurane**	**Sevoflurane/ sevoflurane**	**Total**
Total	264 (100%)	268 (100%)	277 (100%)	246 (100%)	1055 (100%)
Alert	158 (59.8%)	159 (59.3%)	163 (58.8%)	140 (56.9%)	620 (58.8%)
Agitated and distressed	15 (5.7%)	21 (7.8%)	13 (4.7%)	19 (7.7%)	68 (6.4%)
Drowsy	91 (34.5%)	88 (32.8%)	101 (36.5%)	87 (35.4%)	367 (34.8%)

TABLE 109 *Duration of anaesthesia by anaesthetic regimen and gender in the adult study*

	No. of patients											
	Propofol/propofol			**Propofol/isoflurane**			**Propofol/sevoflurane**			**Sevoflurane/sevoflurane**		
	Median duration	**Mean duration**	**Minimum, maximum duration**	**Median duration**	**Mean duration**	**Minimum, maximum duration**	**Median duration**	**Mean duration**	**Minimum, maximum duration**	**Median duration**	**Mean duration**	**Minimum, maximum duration**
Men	40	42	16, 89	35	36	11, 86	36	40	13, 102	38	39	14, 79
Women	34	36	11, 108	33	36	11, 109	33	36	11, 93	36	38	12, 116

Appendix 27

Adverse events in the adult study

The adverse events observed in the adult study are summarised in *Tables 110* to *114*.

TABLE 110 *Incidence of adverse events, other than PONV, by randomisation group in the adult study*

	Total No. of patients	No. of patients				
		0 adverse event	1 adverse event	2 adverse events	3 adverse events	4 adverse events
Adult study	1063	776	235	43	8	1
Propofol/propofol	265	186	62	16	1	0
Propofol/isoflurane	267	202	50	12	3	0
Propofol/sevoflurane	280	222	51	5	1	1
Sevoflurane/sevoflurane	251	166	72	10	3	0

TABLE 111 *Frequency of adverse events, other than PONV, on induction in the adult study*

Adverse event	No. of patients
None	858 (80.7%)
Pain on induction	59 (5.6%)
Excitatory movement during induction	49 (4.6%)
Breath-holding	42 (4.0%)
Coughing	35 (3.3%)
Hiccough	29 (2.7%)
Laryngospasm	14 (1.3%)
Excessive salivation	6 (0.6%)
Unable to intubate or laryngeal mask used	5 (0.5%)
Difficult intubation	4 (0.4%)
Very dry mouth	2 (0.2%)
Technical problem	2 (0.2%)
Drug allergy	1 (0.1%)
Saturations dropped	1 (0.1%)
Arrhythmias	1 (0.1%)
Tachycardia	1 (0.1%)

TABLE 112 *Frequency of adverse events other than PONV in the operating theatre in the adult study*

Adverse event	No. of patients
None	981 (92.3%)
Patient moved a lot during surgery*	34 (3.2%)
Surgery more extensive or prolonged	19 (1.8%)
Saturations dropped	10 (0.9%)
Arrhythmias	3 (0.3%)
Tachycardia	2 (0.2%)
Laryngospasm	2 (0.2%)
Awareness	2 (0.2%)
Minor bleeding	1 (0.1%)
Shivering	1 (0.1%)
Aspiration	1 (0.1%)
Technical problem	1 (0.1%)
Unable to intubate or laryngeal mask used	1 (0.1%)
Coughing	1 (0.1%)
Hyperventilation	1 (0.1%)
Hiccough	1 (0.1%)
Excessive salivation	1 (0.1%)
Vomiting after removal of laryngeal mask	1 (0.1%)

* *Propofol/propofol, 15; propofol/isoflurane, 8; propofol/sevoflurane, 6; sevoflurane/sevoflurane, 5*

TABLE 113 *Frequency of adverse events, other than PONV, in recovery in the adult study*

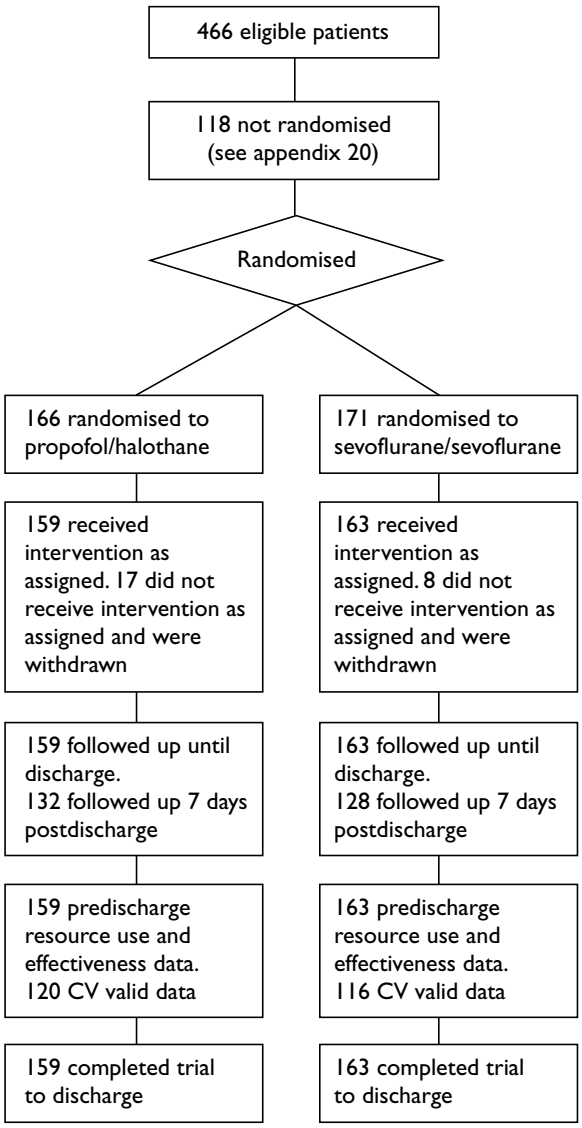
Adverse event	No. of patients
None	1049 (98.7%)
Difficulty breathing	3 (0.3%)
Hypotension	3 (0.3%)
Tachycardia	2 (0.2%)
Hypertension	1 (0.1%)
Bradycardia	1 (0.1%)
Minor bleeding	1 (0.1%)
Uncontrolled pain	1 (0.1%)
Laryngospasm	1 (0.1%)
Shivering	1 (0.1%)

TABLE 114 *Frequency of adverse events, other than PONV, on the ward prior to discharge in the adult study*

Adverse event	No. of patients
None	1043 (98.1%)
Dizziness	5 (0.5%)
Severe headache	4 (0.4%)
Prolonged effect of anaesthetic	3 (0.3%)
Minor bleeding	2 (0.2%)
Uncontrolled pain	2 (0.2%)
Difficulty breathing	2 (0.2%)
Rash	1 (0.1%)
Hypotension	1 (0.1%)

Appendix 28

Profile of the paediatric trial



Appendix 29

Analysis of confounding factors for PONV in the paediatric study

This section displays the association between PONV and other variables which plausibly might be associated with risk. Tables are displayed to check the evenness of the distributions of these potential confounding variables across the randomisation arms. The total numbers of subjects shown in the tables vary slightly, since some of the variables have missing data. Probability values presented with tables refer, unless otherwise stated, to a simple test for heterogeneity among categories. So-called 'exact' tests were employed when appropriate. Probability values are not presented for tables examining the distribution of potential confounding variables among the randomisation categories, as the statistical significance of observed differences is not relevant to the question of confounding.

Age and gender

Table 115 shows the age breakdown of the paediatric population in four nearly equally sized groups (quartiles). These quartiles are employed in a number of tabulations that follow. The age ranges of the quartiles are:

1. < 5.2
2. 5.2 to < 6.6
3. 6.6 to < 9.1
4. ≥ 9.1.

Table 115 shows that there is no clear relationship between PONV and either age or sex in these data.

There were no statistically significant trends with age quartile and no statistically significant differences between boys and girls overall.

Type of surgery

The difference in the occurrence of nausea or vomiting between the ENT and general surgery groups (11% and 8%, respectively) is not statistically significant ($p > 0.4$).

Recovery of awareness

Table 116 shows that (as for adults) children in an agitated state on recovery from anaesthesia were more prone to nausea or vomiting than were others. However, in the paediatric study the observed difference is compatible with being a chance effect.

Duration of anaesthesia

As in the adult study, the risk of PONV depended on the duration of anaesthesia. A similar pattern was found for one or more episodes of vomiting.

TABLE 115 *Occurrence of nausea and vomiting by age quartile and gender in the paediatric study*

	No. of patients				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Total**
Boys					
Total	56 (100%)	52 (100%)	61 (100%)	53 (100%)	222 (100%)
Nausea or vomiting – no	53 (94.6%)	45 (86.5%)	53 (86.9%)	46 (86.8%)	197 (88.7%)
Nausea or vomiting – yes	3 (5.4%)	7 (13.5%)	8 (13.1%)	7 (13.2%)	25 (11.3%)
Girls					
Total	24 (100%)	29 (100%)	20 (100%)	27 (100%)	100 (100%)
Nausea or vomiting – no	21 (87.5%)	28 (96.6%)	20 (100%)	23 (85.2%)	92 (92.0%)
Nausea or vomiting – yes	3 (12.5%)	1 (3.4%)	0 (0%)	4 (14.8%)	8 (8.0%)

TABLE 116 *Occurrence of PONV by awareness on recovery from anaesthetic in the paediatric study*

	No. of patients			
	Alert	**Agitated/ distressed**	**Drowsy**	**Total**
Total	199 (100%)	57 (100%)	65 (100%)	321 (100%)
Nausea or vomiting – no	179 (89.9%)	48 (84.2%)	61 (93.8%)	288 (89.7%)
Nausea or vomiting – yes	20 (10.1%)	9 (15.8%)	4 (6.2%)	33 (10.3%)
χ^2: $p < 0.2$				

TABLE 117 *Occurrence of PONV by tertile of duration of anaesthesia in the paediatric study*

	No. of patients			
	Tertile 1	**Tertile 2**	**Tertile 3**	**Total**
Total	111 (100%)	100 (100%)	111 (100%)	322 (100%)
Nausea or vomiting – no	104 (93.7%)	89 (89.0%)	96 (86.5%)	289 (89.8%)
Nausea or vomiting – yes	7 (6.3%)	11 (11.0%)	15 (13.5%)	33 (10.2%)
χ^2: $p < 0.08$ *(linear trend)*				

Table 117 displays a similar relationship between the duration of anaesthesia and the occurrence of PONV to that found for adults.

ASA grade and previous anaesthetic experience

There was no discernible relationship between either ASA grade or the number of previous anaesthetics received and the occurrence of PONV.

Appendix 30

Adverse events in the paediatric study

The adverse events observed in the paediatric study are summarised in *Tables 118* to *122*.

TABLE 118 *Incidence of adverse events, other than PONV, by randomisation group in the paediatric study*

Anaesthetic regimen	No. of patients			
	Total	0 adverse event	1 adverse event	2 adverse events
Total	322	237	71	14
Propofol/halothane	159	114	39	6
Sevoflurane/sevoflurane	163	123	32	8

TABLE 119 *Frequency of adverse events, other than PONV, on induction in the paediatric study*

Adverse event	No. of patients
None	243 (75.5%)
Excitatory movement during induction	40 (12.5%)
Pain on induction	22 (6.8%)
Coughing	20 (6.2%)
Laryngospasm	4 (1.2%)
Breath-holding	2 (0.6%)

TABLE 120 *Frequency of adverse events, other than PONV, in the operating theatre in the paediatric study*

Adverse event	No. of patients
None	317 (98.4%)
Technical problem	2 (0.6%)
Saturations dropped	1 (0.3%)
Arrhythmias	1 (0.3%)
Shivering	1 (0.3%)

TABLE 121 *Frequency of adverse events, other than PONV, in recovery in the paediatric study*

Adverse event	No. of patients
None	321 (99.7%)
Bradycardia	1 (0.3%)

TABLE 122 *Frequency of adverse events, other than PONV, on the ward prior to discharge in the paediatric study*

Adverse event	No. of patients
None	317 (98.4%)
Haematoma at wound site	2 (0.6%)
Minor bleeding	2 (0.6%)
Abdominal pain	1 (0.3%)

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The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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