Inhalational versus Intravenous Induction of Anesthesia in Children with a High Risk of Perioperative Respiratory Adverse Events

A RANDOMIZED CONTROLLED TRIAL

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Background

- Perioperative respiratory adverse events are experienced by approximately 15% of children undergoing anesthesia with rates as high as 50% reported during some common surgical procedure.

- The incidence of perioperative respiratory adverse events is associated with increased airway reactivity and this association is strongest in individuals with asthma, eczema, a recent upper respiratory tract infection or passive smoke exposure.

Background

- Perioperative respiratory adverse events are associated with an increased probability of prolonged hospital admissions and impact adversely on the patients and their families, surgery waitlists as well as lead to higher healthcare cost.

- The causal relationship between the type of anesthesia induction (Inhalation vs Intravenous) and the risk of perioperative respiratory adverse events is poorly understood.

Background

- The aim of this single-center open-label randomized controlled trial was to assess whether IV induction with propofol or inhalation induction with sevoflurane influenced the likelihood of perioperative respiratory adverse events in high-risk infants and children undergoing minor elective surge.

Methods

- Trial Design
  - Single-center prospective open-label randomized controlled trial
  - Approval was received from the Princess Margaret Hospital for Children Ethics Committee (1787/EP; Subiaco, Western Australia)
  - Informed consent from all participants.

Methods

- Patients : Children up to 9 years who have risk factors of perioperative respiratory adverse events in Minor elective surgery

- Invention : “IV induction group” (IV induction with Propofol)

- Control : “Inhalation induction group” (Inhalation induction with N_2O and Sevoflurane)

Methods

- Primary outcome :
  - The difference in the rate of occurrence of perioperative respiratory adverse events between children receiving IV induction and those receiving inhalation induction of anesthesia.

Methods

- Secondary outcomes :

  - Frequency of the individual respiratory adverse events. Furthermore, in line with clinical importance, these perioperative respiratory adverse events were clustered into two groups; serious (bronchospasm and laryngospasm) and minor (all other respiratory adverse events) respiratory adverse event.

  - Occurrence of respiratory adverse events during the different phases of anesthesia with a particular interest for the induction phase.

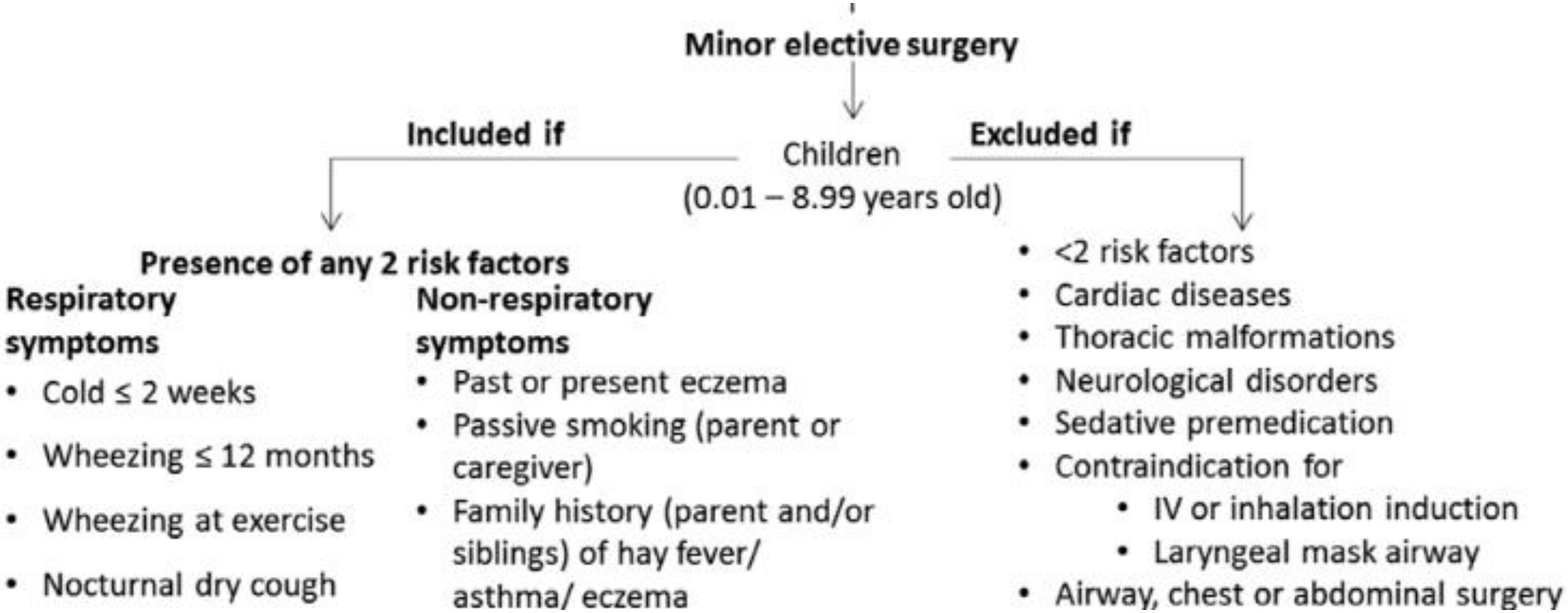
Methods

Table 2. Definition Used for Respiratory Complications Recorded

Perioperative Respiratory Adverse Events	Definition
Laryngospasm	Complete airway obstruction with associated muscle rigidity of the abdominal and chest walls.
Bronchospasm	Increased respiratory effort, particularly during expiration and wheeze on auscultation.
Desaturation < 95%	Less than 95%. The limit of 95% is chosen in line with institutional guidelines based on PACU discharge criteria.
Airway obstruction	Presence of airway obstruction in combination with a snoring noise and/or respiratory efforts.
Severe coughing	A series of pronounced, persistent severe coughs lasting more than 10 s.
Postoperative stridor	High-pitched sound during breathing in the postoperative period

PACU = postanesthesia care unit.

Methods


Minor elective surgery
Children
(0.01 – 8.99 years old)
Included if
Excluded if
Presence of any 2 risk factors
Respiratory symptoms
• Cold ≤ 2 weeks
• Wheezing ≤ 12 months
• Wheezing at exercise
• Nocturnal dry cough
Non-respiratory symptoms
• Past or present eczema
• Passive smoking (parent or caregiver)
• Family history (parent and/or siblings) of hay fever/ asthma/ eczema
• <2 risk factors
• Cardiac diseases
• Thoracic malformations
• Neurological disorders
• Sedative premedication
• Contraindication for
• IV or inhalation induction
• Laryngeal mask airway
• Airway, chest or abdominal surgery

Methods

Table 1. Brief Definition of the Risk Factors Used as Inclusion Criteria in This Trial

Risk Factors	Brief Definition Applied in This Study
Cold ≤ 2 weeks	Signs of runny nose, cough and/or fever (> 38°C) but deemed fit for anesthesia by independent consultant anesthesiologist
Wheezing ≤ 12 months	More than three episodes of wheezing experienced during the past year
Wheezing at exercise	Parentally reported wheezing during exercise
Nocturnal dry cough	A persistent dry night cough observed
Past/Present eczema	Persistent eczema observed in past or currently
Passive smoking	Child exposed to parents/caretakers smoking independent of location, *e.g.*, inside or outside of house
Family history of hay fever/asthma/eczema	At least two family members (any two of parents/siblings/grandparents) with a history of either hay fever or asthma or eczema.

Study protocol : Preoperative

- The randomization process was carried out by an independent statistician and the sealed envelopes handed to the research team.

- Computer generated block randomization was used to assign (1:1) participants randomly to either
  - Intravenous propofol (“IV” group)
  - Inhalational sevoflurane (“inhalational” group)

- No team member was aware of randomization until the anesthesiologist opened the envelope prior to surgery.

Study protocol : Operative

- Intravenous induction is routinely performed while using effective distraction techniques (e.g., verbal and/or visual distractions) when required.

- Topical anesthesia (eutectic mixture of local anesthetic) was also used to reduce the discomfort of inserting the cannula.

- IV induction was achieved with propofol (3 to 5mg/kg) mixed with lidocaine and manually injected slowly to minimize pain.

Study protocol : Operative

- Inhalation induction was carried out with sevoflurane and nitrous oxide.
- Inhalation induction with sevoflurane is achieved by giving the child up to 66% N_2O in oxygen for 20 to 30s, then 8% sevoflurane.
- Typical gas flow ranged between 6 to 8 l/min via a T-piece at induction of anesthesia.
- In line with standard clinical practice, the anesthesiologist in charge of the patient was free to administer a dose of IV propofol as soon as IV access was secured before placing the laryngeal mask airway.

Study protocol : Operative

- In cases where children felt uncomfortable or distressed with either technique of induction, cross-overs to the other group were allowed as a reflection of daily occurrences in pediatric anesthesia.

Study protocol : Operative

- General anesthesia
- Airway device : Laryngeal mask airway
- Maintenance:
  - Sevoflurane
  - Administration of opioids (fentanyl, morphine, alfentanil, pethidine, tramadol, and remifentanil) was left to the discretion of the anesthetist.
- Routine anesthesia monitoring included electrocardiography, noninvasive blood pressure measurements, capnography, and pulse oximetry.

Study protocol : Operative

- The occurrence and rate of each respiratory adverse event were recorded by the attending anesthesiologist during induction, maintenance, and emergence of anesthesia, and by specialized nurses during recovery in the post-anesthesia care unit.

Statistical analysis : sample size

- Sample size calculations were based on the reported difference in the incidence of perioperative respiratory adverse events between children receiving an inhalation induction (38%) and an IV induction (22%) in our previous observational trial.

- A sample size of 128 per group using a two group chi-square analysis, at a 0.05 two-sided significance level provided an 80% power to detect a difference in the rate of perioperative respiratory adverse events between the two groups of at least 16% overall. After allowing for 15% data loss due to unusable or missing data, we aimed to recruit 150 participants in each group.

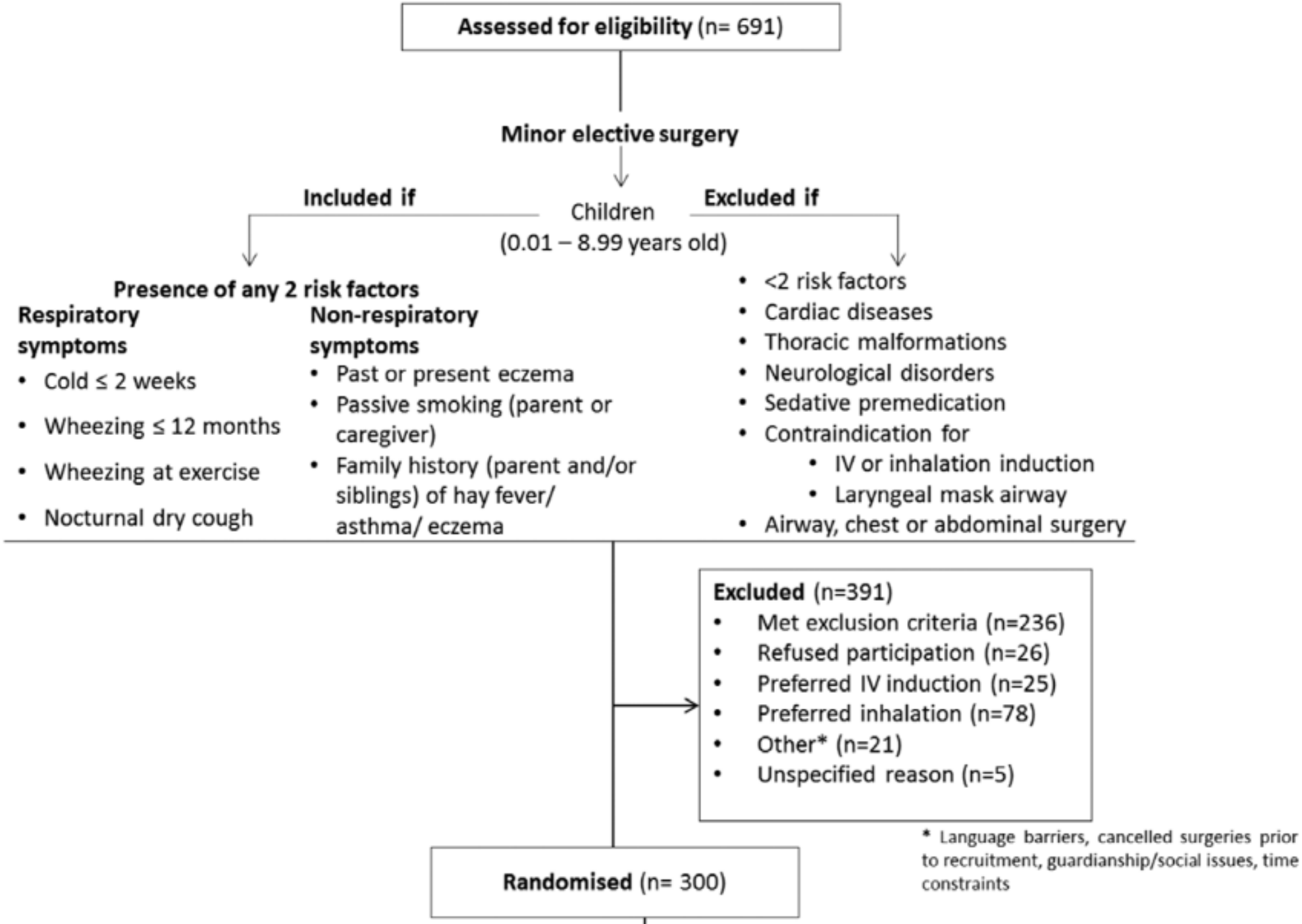
Statistical analysis : sample size

- Statistical analysis was performed with SPSS version 22.0 (IBM Corp., USA) and STATA (Version 13; StataCorp LLC, USA).

- The outcomes are presented as binary variables, and both primary and secondary outcomes were analyzed using Fisher exact test.

- The relative risk and 95%CI reported were calculated according to Altman.

Results


Assessed for eligibility (n= 691)
Minor elective surgery
Included if
Children
(0.01 – 8.99 years old)
Excluded if
Presence of any 2 risk factors
Respiratory symptoms
• Cold ≤ 2 weeks
• Wheezing ≤ 12 months
• Wheezing at exercise
• Nocturnal dry cough
Non-respiratory symptoms
• Past or present eczema
• Passive smoking (parent or caregiver)
• Family history (parent and/or siblings) of hay fever/ asthma/ eczema
• <2 risk factors
• Cardiac diseases
• Thoracic malformations
• Neurological disorders
• Sedative premedication
• Contraindication for
• IV or inhalation induction
• Laryngeal mask airway
• Airway, chest or abdominal surgery
Excluded (n=391)
• Met exclusion criteria (n=236)
• Refused participation (n=26)
• Preferred IV induction (n=25)
• Preferred inhalation (n=78)
• Other* (n=21)
• Unspecified reason (n=5)
* Language barriers, cancelled surgeries prior to recruitment, guardianship/social issues, time constraints
Randomised (n= 300)

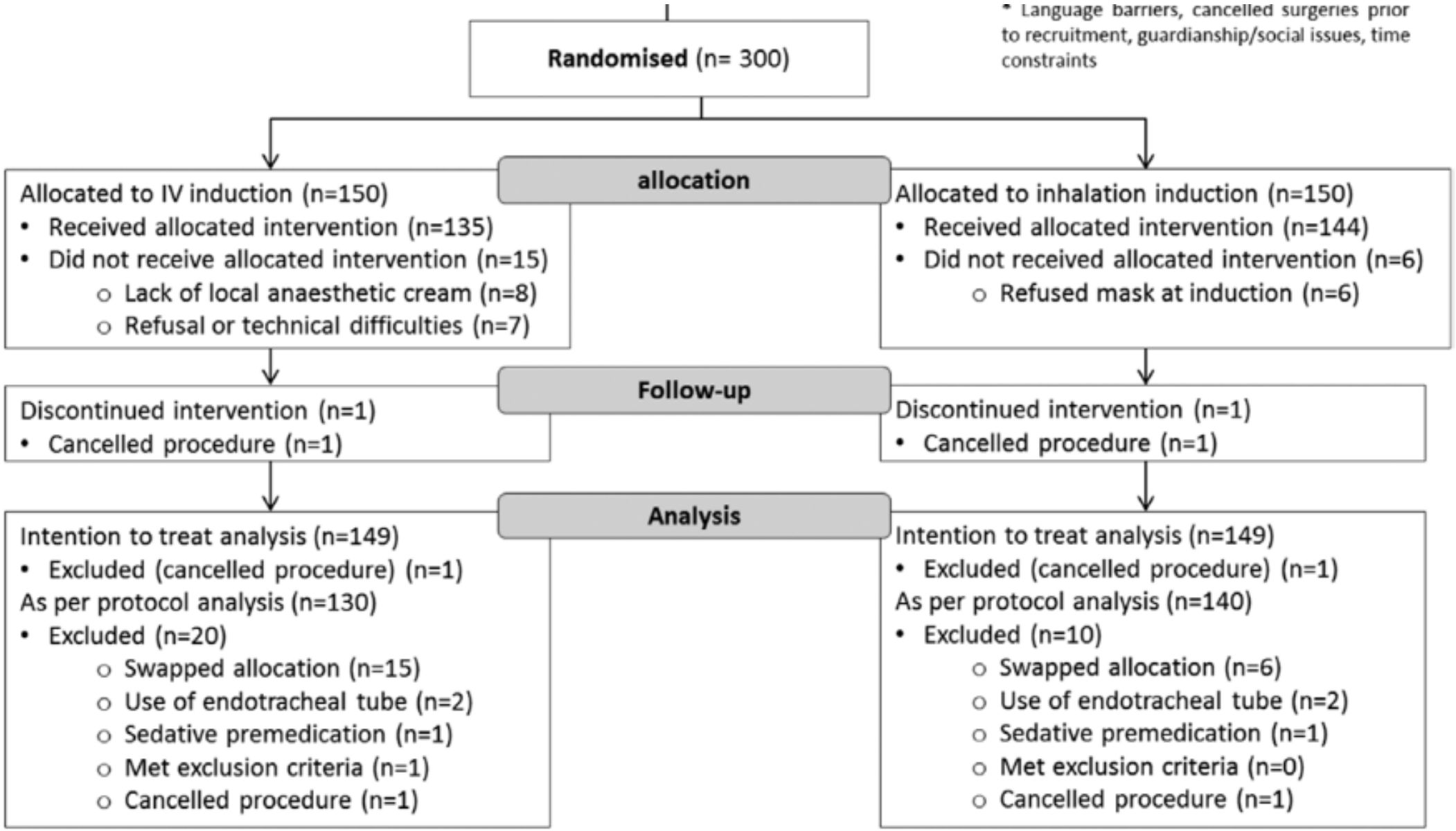

* Language barriers, cancelled surgeries prior to recruitment, guardianship/social issues, time constraints
Randomised (n= 300)
allocation
Allocated to IV induction (n=150)
• Received allocated intervention (n=135)
• Did not receive allocated intervention (n=15)
○ Lack of local anaesthetic cream (n=8)
○ Refusal or technical difficulties (n=7)
Allocated to inhalation induction (n=150)
• Received allocated intervention (n=144)
• Did not received allocated intervention (n=6)
○ Refused mask at induction (n=6)
Follow-up
Discontinued intervention (n=1)
• Cancelled procedure (n=1)
Discontinued intervention (n=1)
• Cancelled procedure (n=1)
Analysis
Intention to treat analysis (n=149)
• Excluded (cancelled procedure) (n=1)
As per protocol analysis (n=130)
• Excluded (n=20)
○ Swapped allocation (n=15)
○ Use of endotracheal tube (n=2)
○ Sedative premedication (n=1)
○ Met exclusion criteria (n=1)
○ Cancelled procedure (n=1)
Intention to treat analysis (n=149)
• Excluded (cancelled procedure) (n=1)
As per protocol analysis (n=140)
• Excluded (n=10)
○ Swapped allocation (n=6)
○ Use of endotracheal tube (n=2)
○ Sedative premedication (n=1)
○ Met exclusion criteria (n=0)
○ Cancelled procedure (n=1)

Table 3. Demographic Data for the Study Cohort for Each Group and According to the Type of Statistical Analysis Carried Out

	Type of Analysis			
	Intention to Treat		As per Protocol	
	IV (N = 149)	Inhalation (N = 149)	IV (N = 130)	Inhalation (N = 140)
Male, %	92, 62%	96, 64%	79, 61%	91, 65%
Median age, yr (min–max)	4.5 (0.9–8·9)	4.3 (0.7–8.8)	4.8 (1.1–8.9)	4.4 (0.7–8.8)
Age group				
0.0–3.0	28 (19%)	39 (26%)	23 (17%)	36 (26%)
3.1–5.0	52 (35%)	54 (36%)	44 (34%)	51 (36%)
5.1–7.0	40 (27%)	37 (24%)	36 (28%)	35 (25%)
7.1–8.9	28 (19%)	19 (12%)	26 (20%	18 (13%)
Median weight, kg (min–max)	18.4 (6.8–40.0)	17.3 (7.8–44.3)	18.7 (6.8–40.0)	17.6 (7.8–44.3)
ASA				
I	98 (66%)	109 (73%)	88 (68%)	101 (72%)
II	47 (32%)	38 (26%)	39 (30%)	37 (26%)
III	4 (3%)	2 (1%)	3 (2%)	2 (1%)
Cold ≤ 2 weeks	49 (33%)	55 (37%)	45 (35%)	51 (36%)
Wheezing 3+ times ≤ 1 yr	27 (18.1%)	22 (15%)	21 (16%)	21 (15%)
Wheezing at exercise	13 (9%)	13 (9%)	12 (9%)	13 (9%)
Nocturnal dry cough	44 (30%)	31 (21%)	40 (31%)	30 (21%)
Past/present eczema	71 (48%)	56 (38%)	63 (49%)	53 (38%)
Passive smoking	71 (48%)	63 (42%)	63 (49%)	60 (43%)
Family history of hay fever	88 (59%)	97 (65%)	75 (58%)	90 (64%)
Family history of asthma	71 (48%)	82 (55%)	59 (45%)	77 (55%)
Family history of eczema	61 (41%)	55 (37%)	50 (39%)	50 (36%)

ASA = American Society of Anesthesiologists physical status; IV = intravenous.

Table 3. Demographic Data for the Study Cohort for Each Group and According to the Type of Statistical Analysis Carried Out

	Type of Analysis			
	Intention to Treat		As per Protocol	
	IV (N = 149)	Inhalation (N = 149)	IV (N = 130)	Inhalation (N = 140)
Male, %	92, 62%	96, 64%	79, 61%	91, 65%
Median age, yr (min–max)	4.5 (0.9–8·9)	4.3 (0.7–8.8)	4.8 (1.1–8.9)	4.4 (0.7–8.8)
Age group				
0.0–3.0	28 (19%)	39 (26%)	23 (17%)	36 (26%)
3.1–5.0	52 (35%)	54 (36%)	44 (34%)	51 (36%)
5.1–7.0	40 (27%)	37 (24%)	36 (28%)	35 (25%)
7.1–8.9	28 (19%)	19 (12%)	26 (20%	18 (13%)
Median weight, kg (min–max)	18.4 (6.8–40.0)	17.3 (7.8–44.3)	18.7 (6.8–40.0)	17.6 (7.8–44.3)
ASA				
I	98 (66%)	109 (73%)	88 (68%)	101 (72%)
II	47 (32%)	38 (26%)	39 (30%)	37 (26%)
III	4 (3%)	2 (1%)	3 (2%)	2 (1%)
Cold ≤ 2 weeks	49 (33%)	55 (37%)	45 (35%)	51 (36%)
Wheezing 3+ times ≤ 1 yr	27 (18.1%)	22 (15%)	21 (16%)	21 (15%)
Wheezing at exercise	13 (9%)	13 (9%)	12 (9%)	13 (9%)
Nocturnal dry cough	44 (30%)	31 (21%)	40 (31%)	30 (21%)
Past/present eczema	71 (48%)	56 (38%)	63 (49%)	53 (38%)
Passive smoking	71 (48%)	63 (42%)	63 (49%)	60 (43%)
Family history of hay fever	88 (59%)	97 (65%)	75 (58%)	90 (64%)
Family history of asthma	71 (48%)	82 (55%)	59 (45%)	77 (55%)
Family history of eczema	61 (41%)	55 (37%)	50 (39%)	50 (36%)

ASA = American Society of Anesthesiologists physical status; IV = intravenous.

Results

Table 4. The Types of Surgery Carried Out and the Number of Participants Recruited Off Each List

	Intention to Treat		As per Protocol	
Type of Surgery	IV (N = 149)	Inhalation (N = 149)	IV (N = 130)	Inhalation (N = 140)
Dental	27 (18%)	18 (12%)	26 (20%)	16 (11%)
ENT	29 (20%)	20 (13%)	24 (19%)	17 (12%)
General	40 (27%)	48 (32%)	36 (28%)	46 (33%)
Plastic	25 (17%)	37 (25%)	18 (14%)	36 (26%)
Other	28 (19%)	26 (17%)	26 (20%)	25 (18%)

ENT = ear, nose, and throat; IV = intravenous.

Results

- Primary outcome :
- Inhalational induction was associated with an increased likelihood of perioperative respiratory adverse events compared with IV induction

Results

- Secondary outcomes :
  - Frequency of Each Perioperative Respiratory Adverse Events : IV induction was associated with a significantly lower incidence of serious and minor perioperative respiratory adverse events compared to inhalational induction.
  - Respiratory Adverse Events over Induction Phase of Anesthesia : Inhalation group were significantly more likely to experience a respiratory adverse event during induction than those receiving an IV induction of anesthesia. The relative risk of respiratory adverse events was not different between induction groups in children who did not report any respiratory symptoms.

Table 5. Perioperative Respiratory Adverse Events Observed over the Perioperative Period (from Induction of Anesthesia to Discharge from PACU) and the Associated Relative Risks, 95% CI, and *P* Values for Each Type of Analysis Carried Out

	Intention to Treat Analysis				
Perioperative Respiratory Adverse Events	IV (N = 149)	Inhalation (N = 149)	RR	95% CI	*P* Value
Any – unadjusted	39 (26%)	64 (43.0%)	1.64	1.18–2.27	0.003
Any – adjusted			1.68	1.21–2.33	0.002
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	3 (2%)	15 (10%)	5.00	1.48–16.91	0.01
Serious (I & II)	3 (2%)	16 (11%)	5.33	1.59–17.92	0.007
III. Coughing	17 (11%)	36 (24%)	2.12	1.25–3.60	0.006
IV. Desaturation	26 (17%)	38 (26%)	1.46	0.94–2.28	0.094
V. Airway obstruction	7 (5%)	25 (17%)	3.57	1.59–8.00	0.002
VI. Stridor (recovery)	2 (1%)	4 (3%)	2.00	0.37–10.75	0.419
Minor (III-VI)	37 (25%)	63 (42%)	1.70	1.22–2.38	0.002
	As Per Protocol Analysis				
	(N = 130)	(N = 140)	RR	95% CI	*P* Value
Any (unadjusted)	34 (26%)	60 (43%)	1.64	1.16–2.32	0.005
Any – adjusted			1.67	1.18 to 2.36	0.004
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	1 (1%)	15 (11%)	13.93	1.87–104.00	0.010
Serious (I & II)	1 (1%)	16 (11%)	14.86	2.00–110.50	0.008
III. Coughing	14 (11%)	34 (24%)	2.26	1.27–4.01	0.006
IV. Desaturation	23 (18%)	37 (26%)	1.49	0.94–2.37	0.089
V. Airway obstruction	7 (5%)	24 (17%)	3.18	1.42–7.14	0.005
VI. Stridor (recovery)	2 (2%)	3 (2%)	1.39	0.24–8.20	0.714
Minor (III-VI)	33 (25%)	59 (42%)	1.66	1.17–2.36	0.005

Adjusted values are for age, sex, American Society of Anesthesiologists physical status, and weight.
IV = intravenous; PACU = postanesthesia care unit; RR = relative risk.

Table 6. Respiratory Adverse Events Observed over the Induction Period and the Associated Relative Risks, 95% CI, and *P* Values for Each Type of Analysis Carried Out

	Intention to Treat Analysis				
Respiratory Adverse Events at Induction	IV (N = 149)	Inhalation (N = 149)	RR	95% CI	*P* Value
Any – unadjusted	16 (11%)	47 (32%)	2.94	1.75–4.94	< 0.001
Any – adjusted			3.06	1.81–5.16	< 0.001
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	0 (0%)	7 (5%)	-	-	-
Serious (I & II)	0 (0%)	8 (5%)	-	-	-
III. Coughing	5 (3%)	23 (15%)	4.60	1.80–11.78	0.002
IV. Desaturation	13 (9%)	23 (15%)	1.77	0.93–3.36	0.081
V. Airway obstruction	1 (1%)	18 (12%)	18.00	2.43–133.11	0.005
Minor (III-V)	16 (11%)	45 (30%)	2.81	1.67–4.75	< 0.001
	≥ 1 Respiratory Symptom Present				
	N = 84	N = 83	RR	95% CI	*P* Value
Any respiratory adverse events	8 (10%)	30 (36%)	3.80	1.85–7.79	< 0.001
	No Respiratory Symptoms Present				
	N = 65	N = 66	RR	95% CI	*P* Value
	8 (12%)	17 (26%)	2.09	0.97–4.51	0.059
	As Per Protocol Analysis				
	IV (N = 130)	Inhalation (N = 140)	RR	95% CI	*P* Value
Any - unadjusted	14 (11%)	45 (32%)	2.98	1.72–5.17	< 0.001
Any - adjusted			3.13	1.81–5.43	< 0.001
I. Bronchospasm	0 (0%)	2 (1%)			-
II. Laryngospasm	0 (0%)	7 (5%)			-
Serious (I & II)	0 (0%)	8 (6%)			-
III. Coughing	5 (4%)	22 (16%)	4.09	1.59–10.47	0.003
IV. Desaturation	11 (9%)	23 (16%)	1.94	0.99–3.82	0.055
V. Airway obstruction	1 (1%)	17 (12%)	15.79	2.13–116.95	0.007
Minor (III-V)	14 (11%)	43 (31%)	2.85	1.64–4.96	< 0.001
	≥ 1 Respiratory Symptom Present				
	N = 72	N = 78	RR	95% CI	*P* Value
Any respiratory adverse events	7 (10%)	29 (36%)	3.82	1.79–8.18	< 0.001
	No Respiratory Symptoms Present				
	N = 58	N = 62	RR	95% CI	*P* Value
	7 (12%)	16 (26%)	2.14	0.95–4.82	0.067

Adjusted values are for age, sex, American Society of Anesthesiologists physical status, and weight. IV = intravenous; RR = relative risk.

Discussion

- An inhalational induction of anesthesia with sevoflurane, were significantly more likely to experience perioperative respiratory adverse events than when IV propofol was used.

- Compared with sevoflurane, propofol is more potent at blunting the reflex bronchoconstriction commonly occurring during mechanical stimulation of the airway

- Furthermore, propofol has been demonstrated to be superior in suppressing laryngeal reflex responses in comparison to sevoflurane, which is also known to maintain the airway in an excitement phase over a longer period of time.

Discussion

- Sevoflurane is a potent bronchodilator via a reduction in parasympathetic nervous tone and an inhibition of the voltage-dependent calcium, potassium, and chloride channels of the bronchial smooth muscle.

- Propofol also has bronchodilatory effects via the reduction in parasympathetic nervous tone, reduction in serotonin 5-hydroxy-tryptamine receptor activity on bronchial smooth muscle cell and an inhibition of adenosine triphosphate induced contraction.

Discussion

- The combination of sevoflurane and nitrous oxide induces an inflammatory response and suppresses the anti-inflammatory response in the local milieu of the airway.

- The combination of sevoflurane with nitrous oxide for anesthesia induction may exacerbate the inflammation, leading to the higher rate of perioperative respiratory adverse events observed in the inhalation compared with the IV group.

- This is supported by further increased incidence of perioperative respiratory adverse events in children with at least one respiratory symptom.

Discussion

- The laryngeal mask airway, the most commonly used airway device in pediatric anesthesia, was the standardized airway device used in this study.

- It could be postulated that the difference between IV and inhalational induction of anesthesia may have been even greater when using an endotracheal tube, since mechanical stimulation of the airway is greater with an endotracheal tube, and therefore increases the risk for laryngeal and bronchial reflex responses.

Limitations

- The major limitation of this trial was an inability to have a double-blinded study design.

- This may lead to investigator bias in which those diagnosing the outcome are aware of the group allocation and/or the study hypothesis.

- However, it is important to note that none of the anesthesiologists who participated in this study were aware of the study hypothesis, therefore this risk of bias was reduced.

Limitations

- Since in routine practice perioperative respiratory adverse events are a composite outcome that requires a degree of clinical judgement.

- We endeavored to ensure that the strict definitions were used by the anesthesiologist and post-anesthesia care unit nurses to record any perioperative respiratory adverse events in our study.

- By doing so, we have minimized the risk of investigator bias and of selective reporting (e.g., including events of soft tissue obstruction in the laryngospasm group).

Limitations

- Analgesia was left to the discretion of the anesthesiologist in both groups.

- Perioperative pain depends on many patient and surgery specific factors and standardization could lead to suboptimal care that we deemed unethical.

- It is well documented that analgesia such as fentanyl and morphine do not impact the risk of major perioperative respiratory adverse events (e.g. laryngospasm), and therefore, we do not believe analgesia choice will have impacted on the study outcomes.

Limitations

- Perioperative respiratory adverse events is dependent on the experience of the anesthesiologist.

- However, all registrars and fellows who participated in the study did so under the direct supervision of a consultant anesthesiologist.

- The latter is composed of a stable group of pediatric anesthesiologists with significant experience in the pediatric field and at our hospital.

Conclusion

- While the results favor IV induction in children at an increased risk of perioperative respiratory adverse events.

- There are patient groups who will still benefit from an inhalational induction, e.g., those with needle phobia or with a history of difficult IV access.

- However, a careful approach, involving meticulous history taking and evidence-based practice, should be the main pillars in tailoring the anesthetic to the individual patient particularly in the children at high risk for respiratory adverse events.

Critical Appraisal

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical Appraisal

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?			✓
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical Appraisal

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes	Can't tell	No ✓
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Critical Appraisal

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	Intension to treat
10. How precise were the results? Were the results presented with confidence intervals?	yes

Critical Appraisal

	Yes	Can't tell	No
11. Do these results apply to my patient?			
• Is my patient so different from those in the trial that the results don't apply?			✓
• How great would the benefit of therapy be for my particular patient?	✓		
12. Are my patient's values and preferences satisfied by the intervention offered?			
• Do I have a clear assessment of my patient's values and preferences?	✓		
• Are they met by this regimen and its potential consequences?	✓		