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Capnography for Monitoring End-Tidal CO_2 in Hospital and Pre-hospital Settings: A Health Technology Assessment

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Conflicts of Interest

There were no conflicts of interest declared.

Table of Contents

Abbreviations

ASA	American Society of Anesthesiologists
CI	confidence interval
CCA	cost-consequence analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CPR	cardiopulmonary resuscitation
ECG	electrocardiogram
$ETCO_2$	end-tidal carbon dioxide
ETT	endotracheal tube
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
PCO_2	partial pressure of carbon dioxide
RCT	randomized controlled trial
RR	risk ratio
ROSC	return of spontaneous circulation
SpO_2	arterial oxygen saturation measured by pulse oximetry
WTP	willingness to pay

Executive Summary

The Issue

Anesthesiologists have been using capnography for decades to monitor end-tidal carbon dioxide ($ETCO_2$) in patients receiving general anesthesia. $ETCO_2$ monitoring using capnography devices has application across several hospital and pre-hospital settings, including monitoring the effectiveness of cardiopulmonary resuscitation (CPR), continuous monitoring of patients in the emergency room or intensive care unit (ICU), during ambulatory transport, to confirm the correct placement of an endotracheal tube (ETT), and monitoring post-operative patients with a history of sleep apnea or who have received high doses of opioids. Depending on the clinical area, the technology is at various stages of adoption.

The growing utility of $ETCO_2$-monitoring technology in diverse clinical settings, the uncertainty regarding the clinical and cost-effectiveness of capnography devices, and access and implementation issues were the main drivers for this health technology assessment (HTA).

Objectives

The objective of this HTA was to assess the clinical and cost-effectiveness of capnography (alone or in combination with other monitoring equipment) compared with no $ETCO_2$ monitoring, standard monitoring (e.g., pulse oximetry, pulse rate, blood pressure, visual assessment), or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings for patients who are undergoing procedural sedation, receiving CPR, or are in serious or critical condition, or for post-operative patients with known obstructive sleep apnea and/or who are receiving high opioid doses. The clinical and cost-effectiveness of the use of capnography in the following patient populations was addressed:

- Adult and pediatric patients undergoing in-hospital procedural sedation
- Adult and pediatric patients receiving CPR in the hospital or pre-hospital setting
- Adult and pediatric patients in serious or critical condition in the hospital or pre-hospital setting
- Adult and pediatric patients with known obstructive sleep apnea and/or who are receiving high opioid doses in post-operative care in the hospital setting.

Capnography was compared with standard monitoring or other forms of non-invasive respiration and ventilation monitoring. Access and implementation issues associated with capnography were also evaluated and discussed.

Methods

A systematic review of the literature was conducted to assess the clinical and cost-effectiveness of capnography.

Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records and daily updates; Embase; the Cochrane Library; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. Search concepts included capnography, capnometry, carbon dioxide monitoring of patients undergoing procedural sedation, CPR, in serious or critical condition, or with obstructive sleep apnea or receiving high opioid doses in post-operative care. Where appropriate, methodological filters were applied to limit retrieval to HTAs, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials or economic studies. Retrieval was limited to English language documents published after January 1, 2005. Conference abstracts were excluded from the

search results. Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/grey-matters). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. Two reviewers screened citations, selected articles for inclusion, extracted data, and performed quality appraisals. If consensus could not be reached, a third party was consulted.

Clinical data were meta-analyzed where possible. Sensitivity analyses were conducted to explore the robustness of the findings. Where meta-analyses were not possible, a narrative synthesis of the results was used to assess the direction and size of the observed effects.

De novo economic evaluations were planned to address the cost-effectiveness of capnography for each population and setting of interest, when possible. All analyses were undertaken from a Canadian ministry of health perspective and included only direct health care costs. The time horizon for each economic analysis spanned from the start of $ETCO_2$ monitoring until hospital discharge. One-way sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses were undertaken to evaluate the robustness of the model to parameter and structural uncertainties.

Citations arising from the literature search were screened by two reviewers to identify studies that contained information related to implementation considerations (for example, access, training, technical support, policies, and procedures) for $ETCO_2$ monitoring using capnography in hospital and pre-hospital settings. This information was summarized narratively, but not systematically reviewed.

Clinical Effectiveness

A total of 2,753 records were identified through the initial database search. Two hundred of these articles were selected for full-text review, of which 23 were selected for inclusion in the clinical review. An additional six articles were included: one was identified through the grey literature search and five were retrieved through subsequent database alerts. Meta-analyses were conducted for two outcomes within the adult patient population undergoing procedural sedation: detection of respiratory failure and change in clinical management. For all other outcomes in the adult procedural sedation population, and in the remaining populations, meta-analyses were not conducted.

Patients Undergoing Procedural Sedation

The results of the clinical analysis suggested that the use of capnography was associated with fewer episodes of respiratory failure (defined as hypoxemia) for adult patients undergoing procedural sedation compared with standard monitoring alone (risk ratio [RR] 0.70; 95% CI, 0.59 to 0.83). The association between the use of capnography and the detection of severe hypoxemia in this population was less clear. Despite a greater detection of respiratory events in the adult population, there was no evidence for statistically significant differences in changes to clinical management, which included the frequency of use of assisted ventilation (RR 0.60, 95% CI, 0.28 to 1.29) and increases in oxygen supplementation (RR 0.92; 95% CI, 0.75 to 1.12), between patients receiving capnography and patients receiving standard monitoring.

For pediatric patients, one study suggested there were no differences in the detection of hypoxemia between capnography and standard monitoring, and one study suggested a reduction in the number of hypoxemia events detected with an immediate (versus a delayed) capnography signal. There was no statistically significant evidence to suggest that capnography

was different from standard monitoring in its ability to detect episodes of hypoventilation and adverse airway and respiratory events, or influence clinical management.

Patients Undergoing Cardiopulmonary Resuscitation

There was limited evidence available to assess the effectiveness of capnography for monitoring adult patients undergoing CPR. For patients experiencing out-of-hospital cardiac arrests, there was evidence for a greater likelihood of return of spontaneous circulation and survival of the acute event for patients monitored with capnography.

No studies of pediatric patients undergoing CPR met the inclusion criteria for the clinical review.

Patients in Serious or Critical Condition

There was limited evidence to assess the effectiveness of capnography for adult patients in serious or critical condition. Evidence suggested that patients monitored with capnography were less likely to experience an unrecognized misplaced ETT compared with patients who were not monitored with capnography. The interpretation of the results for this population was limited due to a lack of reporting of patient characteristics and details of the intervention and comparator in the two included studies.

The studies that met the inclusion criteria for pediatric patients in serious or critical condition included preterm newborns, or newborns that were receiving ventilation and were at high risk of needing resuscitation. One study found a statistically significant difference in the percentage of time that patients spent in an unsafe high or unsafe low $ETCO_2$ range. This finding deserves cautious interpretation, due to the methodological concerns of the study. There were otherwise no statistically significant differences in the detection of respiratory events, detection of respiratory failures, changes in clinical management, survival, or length of stay in hospital found between the intervention and control groups.

Patients With Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

There was no evidence to assess the effectiveness of capnography compared with other forms of monitoring for the detection of respiratory failure for adult patients in post-operative care settings. For other clinical-effectiveness outcomes, compared with standard monitoring, one study found that patients in the post-anesthesia care unit following orthopedic surgery who were monitored with capnography were more likely to have a respiratory event detected and have fewer pauses in breathing while sleeping.

No clinical trials were identified on the use of capnography in pediatric patients in post-operative care.

Harms

For studies that reported harms data, there were no significant differences to note in the occurrence of harms between capnography and other forms of ventilation monitoring.

Cost-Effectiveness

One peer-reviewed costing study was identified that compared the utilization of blood-gas analyses before and after the implementation of standard continuous-sidestream capnography for all mechanically ventilated patients in pediatric ICUs in the United States. Given the limited applicability of this single study, de novo economic evaluations were conducted for each population and setting of interest, with the exception of pediatric patients undergoing CPR or in post-operative care, due to the lack of evidence identified from the clinical review.

For each adult population (i.e., procedural sedation, CPR, serious and critical condition, post-operative), a cost-effectiveness analysis was performed. However, in the pediatric population, different types of economic analyses were undertaken in response to the clinical evidence gathered. A cost-minimization analysis was deemed to be the most suitable method of evaluation for pediatric patients undergoing procedural sedation. For neonates in serious or critical condition, it was possible to evaluate only the relationship between capnography and the confirmation of ETT placement, so a cost-consequence analysis was conducted.

Patients Undergoing Procedural Sedation

In adult patients undergoing procedural sedation, the incremental cost per averted respiratory failure for capnography with standard monitoring, compared with standard monitoring alone, was $413. The model was found to be robust across a range of sensitivity analyses. In pediatric patients undergoing procedural sedation, capnography was associated with an increased expected cost of $50 per patient.

Patients Undergoing CPR

In adult patients requiring out-of-hospital CPR, capnography led to improved survival at a higher cost. The incremental cost-effectiveness ratio (ICER) was $27,269 per life saved. The economic findings were found to be highly sensitive to mortality rates. A secondary analysis was conducted using higher survival rates reported in a study by Phelan et al. from an in-hospital setting, whereby the ICER declined to $4,910 per life saved.

Due to the lack of evidence found in the clinical review for the use of capnography in pediatric patients undergoing CPR, an economic evaluation could not be conducted for this population.

Patients in Serious or Critical Condition

Given the limited clinical evidence for patients in serious or critical condition, exploratory analyses were conducted for the adult and pediatric population separately. Specifically, for the adult population, it was assumed that the relative treatment effects (incidence of respiratory failure) in the capnography group when compared with standard monitoring would be similar to the relative treatment effect that was observed in adult patients receiving procedural sedation. The exploratory analysis showed that capnography improved survival at a lower cost and therefore dominated (i.e., was less costly and more effective) standard monitoring. Sensitivity analysis conducted on the model indicated that capnography remained the dominant strategy, even if the relative treatment effect between capnography versus standard monitoring was less favourable than what was reported in the procedural sedation population.

In the pediatric population, the clinical parameter for misplaced ETT that would not be detected by capnography was informed by a study published in 1995. As it was unclear whether these rates reflect current clinical practice, an exploratory cost-consequence analysis was conducted. Capnography was associated with fewer cases of undetected ETT misplacements (< 1% versus 2.2%) although costs were, on average, $89 per patient compared with $39 in the standard monitoring group.

Patients With Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

The clinical evidence was limited for adults in post-operative care. An exploratory analysis was conducted relying on the same assumption that was previously used: the relative treatment effects for the incidence of respiratory failure were taken from adult patients undergoing procedural sedation. The results showed that patients with capnography monitoring had lower

rates of respiratory failures and at a lower cost than patients with standard monitoring and, therefore, monitoring with capnography dominated standard monitoring.

Due to a lack of clinical evidence, the cost-effectiveness of capnography remains unknown for pediatric patients in post-operative care.

Health Services Impact

Implementation Considerations

Thirty-four citations were identified that contained information regarding barriers, supports, and other implementation issues related to the use of capnography in the hospital and pre-hospital settings. A lack of training and a lack of knowledge of capnography outputs and how to interpret the data to change the course of patient treatment may lead to lower adoption rates for capnography. If the technology and components are easily accessible, always available, and protocols for their use are in place, the greater the likelihood of achieving successful implementation.

Conclusions

For adult patients undergoing procedural sedation, respiratory events were detected more frequently with capnography and fewer patients experienced episodes of hypoxemia compared with standard monitoring. These results, when transferred into the economic evaluation, suggested that capnography offered a reduction in the number of episodes of respiratory failure, but at an additional cost. For adult patients undergoing CPR, the clinical review found that capnography was associated with an increased likelihood of return of spontaneous circulation during out-of-hospital cardiac arrests, resulting in an economic evaluation that suggested capnography was associated with higher survival rates but at an additional cost. In the remaining adult populations, the clinical review found an increased detection of misplaced ETT tubes in adult trauma patients, and an increased detection of respiratory events in patients recovering from orthopedic surgery. These results, however, are based on single studies — each contending with significant sources of biases, which could have influenced their results. Due to the limited clinical evidence, the economic analysis was an exploratory analysis based on the assumption that treatment effects would be consistent with what was observed in patients undergoing procedural sedation; capnography was the dominant intervention for adult patients in serious or critical condition and in post-operative care. These results should be interpreted with caution.

The clinical and economic evidence for the use of capnography in pediatric patient populations is particularly limited. For pediatric patients undergoing procedural sedation, there were no differences in clinical outcomes between capnography and standard monitoring. In terms of immediate versus delayed capnography signals, one study suggested a reduction in the number of hypoxemia events with an immediate signal. Based on the limited clinical evidence for capnography compared with standard monitoring, the economic analysis found that capnography was not cost-effective in pediatric patients undergoing procedural sedation. There was no evidence to assess the clinical or cost-effectiveness of capnography for pediatric patients undergoing CPR or in post-operative care. For pediatric patients in serious or critical condition, the evidence captured in the clinical review assessed the use of capnography in the neonatal ICU; however, there was insufficient evidence to make any conclusions about the effectiveness of capnography in a broader pediatric population.

If capnography is to be successfully implemented in hospitals and pre-hospital settings, barriers and supports will need to be considered.

1. Introduction

End-tidal carbon dioxide ($ETCO_2$) is the level of carbon dioxide that is released at the end of an exhaled breath. $ETCO_2$ levels reflect the adequacy with which carbon dioxide (CO_2) is carried in the blood back to the lungs and exhaled. Available evidence has established that $ETCO_2$ measurement can provide an indication of cardiac output and pulmonary blood flow.[2-4] Non-invasive methods for $ETCO_2$ measurement include capnometry and capnography. Capnometry provides a numerical value for $ETCO_2$. In contrast, capnography delivers a more comprehensive measurement that is displayed in both graphical (waveform) and numerical form. For this reason, capnography is currently the most widely recommended method for monitoring $ETCO_2$[5-8].

Capnography devices are configured as either sidestream or mainstream. In a sidestream configuration, the CO_2 sensor is located in the monitoring device, which is at a distance from the patient. The exhaled CO_2 is diverted from the airway into the device via a sampling tube of six to eight feet in length, which is attached to the breathing circuit fitted to the patient. In the case of a mainstream configuration, the CO_2 sensor and a sampling cell are integrated into a small device that connects directly at the airway, between the breathing circuit and endotracheal tube (ETT). Sidestream devices can monitor both intubated and non-intubated patients, while mainstream devices are most often limited to intubated patients.[9,10] Sidestream measurement has been the most common type of $ETCO_2$ measurement modality in Canadian facilities, even as a number of new, innovative, and ultraportable mainstream capnography devices are becoming available. Whether sidestream or mainstream, capnography devices are available as hand-held portable devices or as a module or component integrated into other medical equipment, such as defibrillators, anesthesiology machines, and patient-monitoring systems.

By using capnography, a patient's ventilation status is monitored in real time. Health care providers are able to identify potential breathing complications (such as airway obstruction, hyperventilation, hypoventilation, or apnea) and respond accordingly with a change in clinical management (for example, providing supplemental oxygen or reassessing the patient).[11-13] Detecting issues at an early stage prompts timely intervention at the onset of an adverse respiratory event, which can help avoid deterioration to a more critical, or fatal, point. A 2011 audit of major airway-management complications in the United Kingdom (UK) estimated that 82% of events resulting in death or brain injury in the intensive care unit (ICU) likely ensued from failure to use capnography in relevant cases.[14] The same audit concluded that half of the deaths that occurred in UK emergency departments could have been avoided had capnography been correctly used and interpreted.[14] However, if capnography is used or interpreted incorrectly, the falsely high or falsely low readings[15] may potentially lead to unnecessary patient interventions.[16] Capnography may also capture an otherwise self-resolving incident of respiratory depression,[17] which might also lead to unnecessary interventions.

$ETCO_2$ monitoring using capnography devices has application across several hospital and pre-hospital settings and, depending on the clinical area, the technology is at various stages of adoption. Anesthesiologists have been using capnography for decades to monitor $ETCO_2$ in patients receiving general anesthesia.[18] The monitoring devices help to prevent or reduce adverse events, such as otherwise undetected respiratory depression and hypoxia.[19-21] In 2012, the Canadian Anesthesiologists' Society (CAS) updated its guidelines to make capnography part of the standard of care in the practice of anesthesia in Canada. Specifically, the CAS guidelines require continuous use of capnography in monitoring patients during general anesthesia and sedation that corresponds to levels 4 through 6 on the Ramsay Sedation Scale.[7]

Despite strong clinical evidence for the use of capnography in general anesthesia and moderate to deep sedation, preliminary scoping discussions suggested there may be a low rate of access or use of this technology in Canada.

More recently, advances in both technology and scientific understanding of the value of $ETCO_2$ monitoring, particularly capnography, have expanded its use beyond anesthesiology. Capnography is also used to monitor the effectiveness of cardiopulmonary resuscitation (CPR) in patients with cardiac arrest;[8,22] for continuous monitoring of patients in the emergency room[11] and ICU;[23,24] during ambulatory transport; and to confirm the correct placement of an ETT.[24-27] The American Heart Association's Advanced Cardiovascular Life Support guidelines, for example, now carry recommendations for the use of quantitative waveform capnography during CPR.[5,28,29] Emerging evidence and expert recommendations also suggest that capnography may be valuable in the early post-operative period.[30-32] Post-operative patients, especially those with a known history of obstructive sleep apnea or who are receiving high doses of opioids for the management of pain, are at an increased risk of adverse respiratory events. Some experts believe that monitoring ventilation with $ETCO_2$ measurement, in addition to pulse oximetry, could improve patient safety and post-operative clinical outcomes.[31,33]

2. The Issue

The growing utility of $ETCO_2$ monitoring technology in diverse clinical settings, uncertainty regarding the clinical and cost-effectiveness of capnography devices, and access and implementation issues were the main drivers for a health technology assessment (HTA).

3. Objectives

The objective of this HTA was to assess the clinical and cost-effectiveness of capnography (alone or in combination with other monitoring equipment) compared with no $ETCO_2$ monitoring, standard monitoring (for example, pulse oximetry, pulse rate, blood pressure, visual assessment), or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings for patients who are undergoing procedural sedation, receiving CPR, or are in serious or critical condition, or for post-operative patients with known obstructive sleep apnea and/or who are receiving high opioid doses. Access and implementation issues associated with capnography were also evaluated and discussed.

3.1 Research Questions

The HTA addressed the following research questions.

3.1.1 Clinical Research Questions

1. For adult patients undergoing procedural sedation, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital settings?
2. For pediatric patients undergoing procedural sedation, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital settings?

3. For adult patients receiving CPR, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings?
4. For pediatric patients receiving CPR, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings?
5. For adult patients in serious or critical condition, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings?
6. For pediatric patients in serious or critical condition, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings?
7. For post-operative adult patients with known obstructive sleep apnea and/or who are receiving high opioid doses, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of respiration and ventilation monitoring in hospital settings?
8. For post-operative pediatric patients with known obstructive sleep apnea and/or who are receiving high opioid doses, what is the clinical effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of respiration and ventilation monitoring in hospital settings?

3.1.2 Economic Research Questions

9. For adult patients, what is the cost-effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in patients undergoing procedural sedation, receiving CPR, or in serious or critical condition, or in post-operative patients with known obstructive sleep apnea and/or who are receiving high opioid doses in hospital or pre-hospital settings?
10. For pediatric patients, what is the cost-effectiveness of monitoring $ETCO_2$ using capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in patients undergoing procedural sedation, receiving CPR, or in serious or critical condition, or in post-operative patients with known obstructive sleep apnea and/or who are receiving high opioid doses in hospital or pre-hospital settings?

3.1.3 Health Services Impact Question

Implementation Issues

What are the implementation considerations (for example, access, training, technical support, policies, and procedures) for $ETCO_2$ monitoring using capnography in hospital and pre-hospital settings?

4. Clinical Review

4.1 Methods

CADTH conducted a systematic review of the literature to assess the clinical effectiveness of capnography compared with no $ETCO_2$ monitoring, standard monitoring, or other forms of non-invasive respiration and ventilation monitoring in hospital or pre-hospital settings for patients who are undergoing procedural sedation, receiving CPR, or in serious or critical condition, or for post-operative patients with known obstructive sleep apnea and/or who are receiving high opioid doses.

4.1.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (with in-process records and daily updates via Ovid); Embase via Ovid; The Cochrane Library (2015, Issue 7), via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. A search for capnography and capnometry was conducted on July 31, 2015. No methodological filters were applied to limit retrieval to a study type. Where possible, retrieval was limited to the human population. Retrieval was limited to English-language documents published between January 1, 2005 and July 31, 2015. Conference abstracts were excluded from the search results. See APPENDIX 1: Literature Search Strategy for the detailed search strategies.

A search for carbon dioxide monitoring of patients undergoing CPR, or procedural sedation, or in serious or critical condition, or with obstructive sleep apnea or receiving high opioid doses post-operatively was conducted on August 12, 2015. Methodological filters were applied to limit retrieval of HTAs, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and controlled clinical trials for carbon dioxide monitoring only. Where possible, retrieval was limited to the human population. Retrieval was limited to English-language documents published between January 1, 2005 and August 12, 2015. Conference abstracts were excluded from the search results. See APPENDIX 1: Literature Search Strategy for the detailed search strategies.

Regular alerts were established to update the searches until March 14, 2016. Studies identified in the alerts and meeting the selection criteria of the review were incorporated into the analysis if they were identified prior to the end of the external peer-reviewer feedback phase (February 25, 2016). Any studies that were identified in the alerts after the peer-reviewer phase, and before March 14, 2016, were described briefly in the discussion, with a focus on discussing the results of those studies compared with the results of the analysis from this systematic review. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/grey-matters), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See APPENDIX 1: Literature Search Strategy for more information on the grey literature search strategy.

4.1.2 Selection Criteria and Method

The eligibility criteria for the clinical research questions (1 to 8) are reported in Table 1.

Inclusion Criteria

Studies suitable for inclusion were selected from those identified through the literature search using the criteria listed below. A 10-year time frame for the literature search was selected based on consensus with content experts and was believed to be sufficient given the evolving nature of the technology and its comparators. Non-randomized study designs in addition to RCTs were considered for inclusion in the review because it was anticipated that due to the nature of the intervention and CADTH's interest in the evidence for safety in addition to effectiveness, there may be limited evidence in the form of RCTs.

Table 1: Inclusion Criteria for the Clinical Review

	Research Questions 1 and 2	Research Questions 3 and 4	Research Questions 5 and 6	Research Questions 7 and 8
Population[a]	Adult (aged ≥ 18 years) and pediatric patients who are sedated for the purposes of tolerating an interventional or diagnostic procedure.[34]	Adult (aged ≥ 18 years) and pediatric patients who are experiencing cardiac arrest and/or absent or abnormal breathing for which CPR is being performed.[35]	Adult (aged ≥ 18 years) and pediatric patients who are in serious or critical condition where vital signs are either unstable or may be unstable and are not within normal limits.[36]	Adult (aged ≥ 18 years) and pediatric patients receiving post-operative care with known obstructive sleep apnea and/or who are receiving high opioid doses.
Intervention	$ETCO_2$ monitoring using capnography (alone or in combination with other monitoring equipment)			
Comparators	• No $ETCO_2$ monitoring • Standard monitoring (e.g., pulse oximetry, pulse rate, blood pressure, visual assessment) • Capnography (comparing between alternative types, such as fixed or portable) • Capnometry • Exhaled CO_2 detector • Esophageal detector device (for patients who are intubated)			
Outcomes	**Primary clinical-effectiveness outcome:** • Detection of respiratory failure (hypoxemia or hypercapnia) **Other clinical-effectiveness outcomes:** • Detection of a respiratory event (i.e., hypoventilation, hyperventilation, apnea, airway obstruction) • Time to detection of a respiratory event • Change in clinical management (i.e., re-evaluate patients, avoid use of more sedative)	**Primary clinical-effectiveness outcome:** • Survival of acute event **Other clinical-effectiveness outcomes:** • Return of spontaneous circulation • Effectiveness of chest compressions • Detection of respiratory failure (hypoxemia or hypercapnia) • Change in clinical management (i.e., continue or withhold chest	**Primary clinical-effectiveness outcome:** • Detection of respiratory failure (hypoxemia or hypercapnia) **Other clinical-effectiveness outcomes:** • Detection of a respiratory event (i.e., hypoventilation, hyperventilation, apnea, airway obstruction) • Time to detection of a respiratory event • Change in clinical management (i.e., re-evaluate patients, provide airway support)	**Primary clinical-effectiveness outcome:** • Detection of respiratory failure (hypoxemia or hypercapnia) **Other clinical-effectiveness outcomes:** • Detection of a respiratory event (i.e., hypoventilation, hyperventilation, apnea, airway obstruction) • Time to detection of a respiratory event • Change in clinical management (i.e., re-evaluate patients, provide airway support)

	Research Questions 1 and 2	Research Questions 3 and 4	Research Questions 5 and 6	Research Questions 7 and 8
		compressions, re-evaluate patients)		
	• Survival to hospital discharge • Discharge with full neurological functioning • Hypoxia • Organ damage • Length of stay in hospital • Correct placement of an endotracheal tube[b]			
	Harms: • Displacement of a ventilation or intubation tube[b] • Adverse events related to the capnography device (i.e., misinterpretation of capnography readings, capnography device malfunction)			
Study Setting	Patients receiving care in hospital (emergency department, endoscopy suite, cancer ward)	Patients receiving care in hospital or pre-hospital settings. Pre-hospital settings include care provided by health care providers as first responders and during ambulatory transport		Patients receiving care in hospital
Study Design	Randomized controlled studies and non-randomized controlled studies (non-randomized controlled trials, quasi-experimental studies, controlled before and after studies, cohort studies, case-control studies)			

CO_2 = carbon dioxide; CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide.
[a] Patients who may fall into more than one defined population will be included.
[b] For patients who are intubated.

Exclusion Criteria

Duplicate publications, narrative reviews, case series, case reports, editorials, and conference abstracts were excluded. Studies were excluded if they did not meet the selection criteria, took place outside of the hospital or pre-hospital setting, or if preliminary results were reported only in abstract form. If the primary objective of the study was to assess the diagnostic accuracy of capnography (for example, in detecting the correct placement of an ETT or feeding tube, or to assess the agreement between $ETCO_2$ and other measures of ventilation) without assessing the impact on clinical outcomes or patient management, the study was excluded. Studies were excluded if they were not published in English.

Selection Method

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search. Full-text articles of the studies remaining after the initial screen were retrieved and independently reviewed based on the selection criteria. Any disagreements arising from the full-text screen were resolved through discussion, or by referral to a third party. The study selection process is presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart. Screening checklists used to guide study selection for research questions 1 to 8 can be found APPENDIX 3: Full-Text Screening Checklist.

4.1.3 Data Extraction

Data were extracted independently by one reviewer and verified for accuracy and completeness by a second reviewer. Any disagreements were resolved through discussion, or by referral to a third party. Standardized data extraction forms were designed a priori to document and tabulate the description of the publications; relevant study characteristics; participant eligibility criteria; intervention characteristics; comparator characteristics; outcome characteristics; intervention and comparator group characteristics; and results, including primary analysis and results of any

subgroup analyses. A Microsoft Excel spreadsheet was used to manage data extraction for each question within the clinical effectiveness review. The utility of the data extraction forms was initially pilot tested by two reviewers. In the pilot phase, the data from two studies for each of the four populations (if available) were extracted by each reviewer independently and then compared. Any disagreements were resolved through discussion until consensus was reached. Minor amendments were made to the data-extraction forms during pilot testing to accommodate the extraction of important study and patient characteristics, and for ease of use. Data extraction then proceeded, with one reviewer extracting all data and the second reviewer verifying all extractions. Data from figures were not used if the data points were not explicitly labeled. Data-extraction forms for research questions 1 to 8 can be found in APPENDIX 4: Data Extraction Form — Clinical Review.

4.1.4 Outcomes and Prioritization

For research questions 1, 2, and 5 to 8, the primary outcome was the detection of respiratory failure (i.e., hypoxemia or hypercapnia). Hypoxemia was defined according to an oxygen saturation (SaO_2) or a partial pressure of oxygen threshold (defined, for example, as $SaO_2 < 90\%$[20,37-39]). All study-specific definitions of hypoxemia and hypercapnia were extracted. For research questions 3 and 4, the primary outcome was survival of the acute event. Other outcomes of interest across all populations included survival to hospital discharge; change in clinical management (e.g., continue or withhold chest compressions, re-evaluate patients); discharge with full neurological functioning (defined, for example, as cerebral performance category);[40] detection of a respiratory event (e.g., respiratory depression defined, for example, as $ETCO_2 \geq 50$ mm Hg or change from baseline of ≥ 10%;[19] apnea (defined, for example, as apnea for 20 seconds);[41] hypoxia; return of spontaneous circulation (ROSC) (research questions 3 and 4), and effectiveness of chest compressions (research questions 3 and 4). While each outcome is listed as an individual measure of clinical effectiveness, it is important to recognize that each exists as part of a clinical pathway that progresses from obtaining the test information, interpreting the test information, making a patient-management decision and, finally, to affecting patient health outcomes.[42,43] All patients experience a different path from the interpretation of test results to clinical outcomes;[44] therefore, the inclusion of outcomes along the entire clinical decision pathway is intended to strengthen our assessment of clinical effectiveness.[42]

4.1.5 Quality Assessment and Risk of Bias Assessment

One reviewer independently assessed the quality of each study, and the assessments were subsequently verified by a second reviewer. Disagreements were resolved through discussion. The Cochrane Collaboration's tool for assessing risk of bias[45] was used for the assessment of randomized controlled studies. For assessment of the methodological quality of non-randomized studies, the Scottish Intercollegiate Guidelines Network SIGN 50 checklists for cohort[46] and case-control studies[47] were used. The quality assessment was performed at the study level. No numerical scores were calculated; instead, a narrative synthesis of the quality and risk-of-bias assessment for each included study was conducted and is presented according to the clinical research question. These summaries are accompanied by comprehensive tables that present the strengths and limitations of each study following the criteria used to conduct the critical appraisal. Studies were not excluded on the basis of the critical appraisal results.

4.1.6 Data Analysis Methods

A narrative synthesis of study characteristics and patient characteristics for each included study was conducted and presented according to clinical research question. These summaries were accompanied by comprehensive data tables to ensure consistency of presented information across all studies and to facilitate study comparisons by the reader.

Tables were created to summarize the study and patient characteristics separately for the randomized and non-randomized studies of each population.

Data tables were created for each outcome listed in Table 1. Due to the variability in terminology used between studies, study-specific terminology is reported in the cells of the tables, and the definition of the outcome is reported as a corresponding footnote in the table. Each data point extracted from the included studies was categorized under the appropriate outcome heading in our review on the basis of how the outcome was measured or defined, and not necessarily the term used within study reports to describe the outcome. For example, Slagelse 2013[48] defined hypoxia as an arterial oxygen saturation measured by pulse oximetry (SPO_2) reading of less than 92%. However, for the purposes of our review, an outcome measure based on a pulse oximetry value is indicative of hypoxemia, and would therefore be included as a data point within our primary outcome, hypoxemia.

Data were deemed sufficient for meta-analysis (i.e., low statistical and clinical heterogeneity) for two outcomes, detection of respiratory failure (defined as hypoxemia) and change in clinical management, within the adult patient population undergoing procedural sedation (research question 1). Studies typically reported more than one measure of hypoxemia based on a pulse oximetry (SpO_2) threshold. Outcomes deemed appropriate to pool for the clinical analysis as indicative of hypoxemia were those outcomes of between $SpO_2 < 93\%$ and $SpO_2 < 90\%$. Severe hypoxemia was defined by SpO_2 measures between $SpO_2 < 88\%$ and $SpO_2 < 81\%$. These thresholds were established based on the availability of evidence and in consultation with clinical experts. If studies reported multiple measures of hypoxemia, measures meeting these criteria were included in the pooled analysis; all other outcomes were reported individually in a separate data table. For all other outcomes in the adult procedural-sedation population and in the remaining populations, meta-analysis was deemed inappropriate due to the limited number of studies available and the heterogeneity of the clinical and methodological characteristics of the included studies. In those cases, corresponding data tables are presented and are accompanied by a narrative synthesis to assess the direction and size of observed effects.

Meta-analyses were carried out using Cochrane Review Manager software (version 5.3) to derive pooled estimates for hypoxemia and change in clinical management. Only randomized study designs were included in the meta-analysis due to the availability of outcome data and the methodological heterogeneity between randomized and non-randomized study designs. Meta-analyses were performed using a random effects model. Forest plots were presented for all evidence syntheses to supplement reported estimates. All outcomes were dichotomous and were summarized using risk ratios (RRs) and 95% confidence intervals (CIs).

Between-study heterogeneity was assessed using the I^2 test, with $I^2 \geq 75\%$ indicating considerable heterogeneity across trials, as suggested by the *Cochrane Handbook for Systematic Reviews of interventions*.[49] Cochran's Q statistic (based on chi-squared, where $I^2 = [Q - \text{degrees of freedom}] \div Q$) was used to test for the presence of heterogeneity based on a level of significance of 10%. Sufficient data were not available to conduct any subgroup analyses of interest identified a priori in the review protocol (i.e., study design, setting of care, type of device, patient characteristics, and details of procedure).

Sensitivity analyses were conducted to explore the impact on pooled results of including or excluding studies based on different eligibility criteria. Specifically, two sensitivity analyses were performed based on:

1. Procedures performed (i.e., including or excluding studies with surgical abortion). Patients undergoing surgical abortion are typically young healthy females who would likely require

different amounts of sedative and have different responses to the sedative used compared with other procedures. Other studies such as those involving patients undergoing endoscopy or orthopedic procedures would include both male and female patients who may have a more diverse medical profile.

2. Differences in sedative type used (i.e., including or excluding studies using midazolam and meperidine or fentanyl). Propofol is a highly titratable sedative that is commonly used in procedural sedation either alone or in combination with other drugs. Studies that use other sedatives instead of propofol as part of their sedation regime may change the likelihood of experiencing a respiratory event.

4.2 Results

4.2.1 Quantity of Research Available

A total of 2,753 records were identified through the initial database search. Two hundred of these articles were selected for full-text review, of which 23 were selected for inclusion in the clinical review. An additional six articles were included: one was identified through the grey literature search and five were retrieved through subsequent database alerts. One study was identified in the final database alert, and was therefore not included in the main analysis. This study was described narratively in the discussion. The PRISMA flowchart representing the process used to identify and select studies for the review and the main reasons for exclusion can be found in APPENDIX 5: Study Selection Flow Diagram — Clinical Review. The list of the excluded studies and the reasons for exclusion are provided in Table 17 of APPENDIX 6: List of Studies Excluded From the Clinical Review and Reasons For Exclusion.

4.2.2 Study Characteristics

Details of the study characteristics for each research question are summarized below. Additional detail can be found in APPENDIX 7: Detailed Study Characteristics.

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

A total of seven randomized and 10 non-randomized studies met the inclusion criteria for the clinical review for adult patients undergoing procedural sedation (Table 1). Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication

The publication year of the studies ranged from 2005[50] to 2016,[51,52] and the greatest number of studies were conducted in the US (n = 9)[19,46,50,52-58] followed by Germany (n = 4),[20,38,51,59] with one study each from Denmark,[48] Japan,[60] the Netherlands,[61] and Spain.[62]

Study Size

Among the randomized studies, sample sizes ranged from 132 in Deitch 2010[19] to 760 in Beitz 2012.[38] For the non-randomized studies, sample sizes ranged from 20[59,60] or 21[56] to up to 966 patients in Barnett 2016.[52]

Study Setting

All studies took place in a hospital setting, with four in the emergency room,[19,55,57,58] eight in the endoscopy unit,[20,38,48,51,52,54,59,62] and one in an outpatient clinic.[61] The hospital department setting was unclear in four studies.[50,53,56,60]

Study Design

Randomized Studies

All randomized studies assessed the effectiveness of capnography compared with standard monitoring according to one of the following three study design schemes:

- Standard monitoring with capnography visible versus standard monitoring alone.[20,48,61]
- Standard monitoring with capnography visible versus standard monitoring with capnography not visible.[19,38,51]
- Standard monitoring with capnography not visible (respiratory events detected were signalled by an independent observer within 5 to 10 seconds of onset) versus standard monitoring with capnography not visible (respiratory events detected were not signalled by an independent observer unless apnea occurred lasting more than 30 seconds).[54]

Non-randomized Studies

Seven of the 10 non-randomized studies assessed the effectiveness of capnography compared with standard monitoring. All seven studies were prospective cohort studies, one of which was a before and after study where a group of patients were monitored before the implementation of capnography and a group of patients were monitored after the implementation of capnography.[52] The remaining six studies involved patients being monitored by standard monitoring and capnography for which the capnography monitors were not visible to the treatment team — a research assistant or study investigator recorded the data observed by each monitoring method.[50,55,57-59,62] It was unclear if monitoring device values were visible to the treatment team in Cacho 2010.[62] The remaining three non-randomized studies compared capnography to either rainbow acoustic monitoring (RAM),[56] or to transcutaneous capnography.[53,60] These three studies followed a similar protocol to those that included a standard monitoring group in that they were prospective cohort studies where device data were either electronically or manually recorded and then retrospectively analyzed. In Tanaka 2014[56] all patients were monitored with RAM and capnography during their procedure. Waveform and sound files were then retrospectively analyzed and compared. In Kusinski 2012[60] all patients were monitored with transcutaneous capnography and $ETCO_2$ capnography, but it was unclear if the monitor values were visible to the treating team. In De Oliveria 2010,[53] the treating team was blinded to transcutaneous capnography data, but $ETCO_2$ capnography data were visible.

Intervention

In one study, the type of capnography device used was not reported.[52] In the remaining included studies, the capnography devices used for $ETCO_2$ monitoring were one of the following:

- Capnostream 20[19,38,51,54,56,59,61]
- Microcap[20,60,62]
- LIFEPAK 12 defibrillator/monitor[58]
- Capnomac Ultima[53]
- Nellcor OxiMax NPB-75[55,57]
- Nellcor OxiMax NPB-70[50]
- Phillips MP20 monitor.[48]

All devices were sidestream, multi-parameter models (for example, measuring two or more of the following parameters: $ETCO_2$, SpO_2, respiratory rate, electrocardiogram (ECG), temperature), connected to the patient via an oral or nasal cannula. The devices are portable, some of them hand-held (Microcap, Nellcor OxiMax NPB-75, Nellcor OxiMax NPB-70), and all suitable for adult and pediatric patients. Neonatal use was specified for five of the seven devices (Capnostream 20, Microcap, Nellcor OxiMax NPB-75, and Philips MP20, Nellcor OxiMax

NPB-70). A detailed description of the capnography devices used in the included studies can be found in Table 28 of APPENDIX 8: Details of the Capnography Devices.

Comparator

Randomized Studies

Standard monitoring within the randomized studies always included pulse oximetry,[19,20,38,48,51,54,61] and, depending on the study and the level of detail provided for the study protocol, standard monitoring may have also included clinical observation,[20,38,48,51,61] heart rate,[20,38,48,54] pulse rate,[19,38] blood pressure (continuous,[19,48,51] every three minutes,[20,38] or every five minutes[54]), and ECG monitoring.[20,38,48,51]

Non-randomized Studies

When standard monitoring was the comparator of interest in the included studies, standard monitoring always included pulse oximetry,[50,55,57-59,62] and some studies also included other forms of monitoring such as: heart rate,[58,59] electrocardiography,[50,59] bispectral index,[50,53] vital signs,[55,57] clinical observation,[62] cardiac rhythm, respiratory rate, and blood pressure.[50,58] Standard monitoring was not described in the one study.[52]

RAM, using the Rad-87 (Masimo Corporation, software version 7805), was the comparator of interest in one study.[56] RAM is a non-invasive, multi-parameter bedside-monitoring device that has the capacity to measure several patient parameters including: acoustic respiration rate, SpO_2, pulse rate, and perfusion index.[63]

In two studies,[53,60] transcutaneous capnography using the TOSCA 500 (Linde Medical Sensors AG) was the comparator of interest. Transcutaneous capnography is a non-invasive, multi-parameter portable monitoring device that has the capacity to measure several patient parameters including: transcutaneous partial pressure of carbon dioxide (PCO_2), SpO_2, and pulse rate.[64]

Outcomes Measured

Primary and secondary outcomes were explicitly identified as such in six randomized and one prospective cohort study.[20,38,48,51,54,59,61] In the remaining studies, [19,50,52,53,55-58,60,62] the outcomes measured were not identified as primary or secondary, but were reported as being measured. Reported outcomes included hypoxemia,[20,38,51,52,54,59,61] hypoxia,[48] oxygen desaturation,[38,59] apnea,[20,50,51,54,59] duration of detected apnea,[59] bradycardia,[20,38,51,59] hypotension,[38,51,59] change in clinical management,[20,38,48,52,54,59,61] number of complications,[59] recovery time,[38,59] hypoventilation,[53,62] respiratory depression,[55,57] adverse events,[52,55,57] and clinically important acute respiratory events.[58]

Statistical Analysis Plan

The statistical analysis plan for the randomized studies involved an assessment of the primary outcome between intervention and comparator groups using a chi-square test,[19,38,48,51,54,61] or Fisher's exact test.[20] All studies reported patient discontinuation from the study following randomization. Patients were excluded from the analysis due to technical device failure,[61] inadequate preparation for the procedure,[20] withdrawal of consent,[38] > 35% loss of data,[19] wrong procedure,[51] or a combination of factors (no data, double participation, withdrawn prior to procedure, withdrew consent, and device problems).[48] All studies, except for Klare 2016,[51] were based on a per-protocol clinical efficacy analysis where analyses were performed on patients who remained in the study until completion. Klare 2016[51] performed an intention-to-treat analysis for all outcome measures, and Qadeer 2009[54] performed an intention-to-treat analysis for an assessment of safety outcomes. In addition to the primary analysis, multivariate

regression analyses were performed as supportive analysis in three studies[20,38,54] to control for the following variables: age,[20,54] sex,[54] body mass index (BMI),[20,54] lung disease,[38] history of sleep apnea,[20] baseline oxygen saturation,[38] type of procedure,[54] and sedative dose.[20,54] The majority of prospective cohort studies did not perform any formal statistical analyses for an assessment of the outcomes of interest for this review.[50,55,57,58,60,62] Comparative statistical analyses on outcomes of interest for this review were performed in four studies using a chi-square test,[53] Fisher's exact test,[52] an exact unconditional McNemar's test,[59] and sensitivity and specificity formulas.[56] In addition to the primary analysis, multivariate regression analyses were performed as supportive analysis in one study[52] to control for the following variables: age, sex, body mass index, ethnicity, and American Association of Anesthesiologists (ASA) score.[52]

Study Funding

Manufacturers supplied the capnography devices in five randomized studies[19,38,48,51,54] and two prospective cohort studies,[58,59] and a rainbow acoustic monitor in one study.[56] Three authors in two studies received material support for research purposes from the capnography device manufacturer,[38,51] and in one study, one contributing author received an educational grant from a capnography manufacturer.[54] In one study, a grant was received by the rainbow acoustic monitoring manufacturer.[56] Public and private funding was received in one study,[48] state funding in another,[61] and a university grant[53] and an innovation grant were received[52] in others. No funding was specified in the remaining studies.[19,20,50,55,57-60,62]

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Two randomized and two non-randomized studies met the inclusion criteria for the clinical review for pediatric patients undergoing procedural sedation (Table 1).[65-68] Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication

The studies were published in 2006,[65] 2007,[66] 2011,[67] and 2015.[68] All studies were conducted in the US.

Study Size

Sample sizes were generally similar between studies: 125 to 163.[65-68]

Study Setting

One study took place in the pediatric emergency department of a tertiary care academic centre,[68] while the three other studies took place within the endoscopy unit,[65] imaging department,[67] or emergency department[66] of a tertiary pediatric hospital.

Study Design

Randomized Studies

The two randomized studies assessed the effectiveness of capnography compared with standard monitoring according to the following study design schemes:

1. Standard monitoring with capnography visible versus standard monitoring with capnography not visible.[68]
2. Standard monitoring with a capnography-based signal (waveform absent for > 15 seconds) from an independent observer versus standard monitoring with a delayed (waveform absent for > 60 seconds) capnography signal from an independent observer.[65]

Non-randomized Studies

The two non-randomized studies assessed the effectiveness of capnography compared with standard monitoring. Both non-randomized studies were prospective cohort studies that

involved all patients being monitored by standard monitoring and capnography, during which a research assistant or study investigator was present to record the data observed by each monitoring method.[66,67] It was unclear if monitoring device values were visible to the treatment team in Anderson 2007.[66]

Intervention

The capnography devices used for $ETCO_2$ monitoring in the included studies were one of the following:

- Nellcor OxiMax NPB-75[68]
- Phillips MP20 monitor[65]
- Capnocheck II[66]
- N-85 hand-held capnography/pulse oximeter.[67]

All devices were sidestream, portable, and multi-parameter models (measuring two or more parameters, such as $ETCO_2$, SpO_2, respiratory rate, heart rate, ECG, temperature), connected to the patient via an oral or nasal cannula. Three of the four devices (Capnocheck II, N-85 capnography/pulse oximeter, and Nellcor OxiMax NPB-75) were hand-held and suitable for adult and pediatric patients. Neonatal use was specified for three of the four devices (N-85 capnography/pulse oximeter, Nellcor OxiMax NPB-75, and Philips MP20). A detailed description of the capnography devices used in the included studies can be found in Table 29 of APPENDIX 8: Details of the Capnography Devices.

Comparator

Randomized Studies

Standard monitoring within the randomized studies included impedance plethysmography,[68] pulse oximetry,[68] electrocardiography,[65,68] vital signs (heart rate, respiratory rate, blood pressure),[65,68] visual assessment,[65] and depth of sedation.[65]

Non-randomized Studies

The data obtained from standard monitoring were the comparator data of interest in the prospective cohort studies. Standard monitoring followed published sedation guidelines in Kannikeswaran 2011,[67] and involved a four-member team of clinicians monitoring the patient (including vital signs and depth of sedation) in Anderson 2007.[66]

Outcomes Measured

Primary and secondary outcomes were explicitly stated in the two randomized studies and included hypoventilation without hyperventilation,[68] staff interventions,[65,68] oxygen desaturations,[65,68] persistent hypoventilation,[68] timely interventions,[68] abnormal ventilation,[65] and adverse events.[65] Primary and secondary outcomes were not explicitly identified as such in the two prospective cohort studies but, in addition to the outcomes already stated, also measured hypoxia,[67] acute respiratory events,[67] and apnea.[66]

Statistical Analysis Plan

The statistical analysis plan for the randomized studies involved a comparison of the primary outcome between intervention and control groups using a chi-square test,[68] or Fisher's exact test.[65,68] One study reported patient discontinuation following randomization due to crying for more than 20% of the sedation period, age, and cannula obstruction,[68] resulting in a per-protocol efficacy analysis. Lightdale 2006[65] performed an intention-to-treat analysis. In addition to the primary analysis, multivariate regression analyses were performed as supportive analysis in both studies to control for the following variables: age,[65,68] sex,[65,68] ethnicity,[65,68]

procedure type,[65] duration of procedure,[65,68] provider,[68] respiratory rate,[68] baseline oxygen saturation and $ETCO_2$,[65] use of shoulder roll at the start of the procedure,[68] level of sedation,[65] length of sedation,[68] and sedative dose.[65,68] Both prospective non-randomized studies summarized outcomes with descriptive statistics; no formal statistical analyses were conducted for the outcomes of interest for this review.[66,67]

Study Funding

Manufacturers supplied the nasal cannulas in one prospective cohort study,[67] and the capnography filter lines and capnography device in one RCT.[65] A foundation clinical research grant was received in the other prospective cohort study,[66] and a National Institutes of Health grant in the other RCT.[68]

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

One non-randomized study met the inclusion criteria of the clinical review for adult patients undergoing CPR (Table 1).[1] Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication

Chen 2015[1] was conducted in Taiwan.

Study Size

The sample size of the study was 1,113 patients.[1]

Study setting

The study included all patients who experienced an out-of-hospital cardiac arrest and were subsequently transferred to one of several possible settings: medical centre, regional hospital, local hospital, or clinic.[1]

Study Design

The non-randomized study was an observational retrospective cohort study.[1] The study cohort was generated from a random sample of patients covered by a national health insurance program. Patients were classified as having (or not having) received $ETCO_2$ and, subsequently, a propensity-matched sample in a ratio of 1:20 was selected for the primary analysis.[1]

Intervention

No information was provided for the capnography device that was used in the study.[1]

Comparators

No information was provided to describe what standard monitoring consisted of in this study.[1]

Outcomes Measured

The primary and secondary outcomes were not explicitly stated as such in this study; however, outcomes included: sustained ROSC[1] and survival to hospital discharge.[1]

Statistical Analysis Plan

A propensity score was used to select patients for the intervention and control group, controlling for possible confounders: age, sex, year, level of urbanization, health care institute type, socioeconomic status, CPR duration, and attempted defibrillation. Conditional logistic regression was then used to calculate the odds of detecting outcomes between the intervention and comparator groups.[1]

Study Funding
No study-specific funding source was noted in the study report.[1] Authors stated they did not have any competing interests.[1]

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation
No studies met the inclusion criteria of the clinical review for pediatric patients undergoing CPR (Table 1).

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition
Two studies (a retrospective cohort study[69] and a prospective cohort study[70]) met the inclusion criteria of the clinical review for of adult patients in serious or critical condition (Table 1). Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication
The studies were published in 2005[70] and 2014,[69] and both were conducted in the US.

Study Setting
The studies took place in an emergency department: one in a tertiary care hospital,[69] and one in a level-one trauma centre.[70]

Study Size
Sample sizes were similar between studies (153[70] and 169[69]).

Study Design
Both studies included patients who arrived at the emergency department having been intubated out of hospital. The retrospective cohort study[69] undertook a chart review for patients having spent at least two hours boarding in the emergency department. Each patient was classified as having (or not having) received each of six individual interventions of interest, including $ETCO_2$ monitoring. The prospective cohort study[70] involved an assessment of patients upon arrival at the emergency department for correct placement of the ETT, method used to determine ETT position, and whether $ETCO_2$ monitoring was used in the field and upon arrival at the emergency department.

Intervention
No information was provided about the capnography device used in either study.[69,70]

Comparators
No information was provided to describe what standard monitoring consisted of in either study.[69,70]

Outcomes Measured
In the retrospective cohort study,[69] the primary and secondary outcomes were not explicitly identified as such; however, the outcomes measured included mortality and ventilator-associated pneumonia. In the prospective cohort study,[70] the primary outcome was the rate of unrecognized misplaced ETT. Other outcomes included mortality, discharge location, and neurological impairment.[70]

Statistical Analysis Plan

In the retrospective cohort study,[69] the relationship between $ETCO_2$ monitoring and mortality and ventilator-associated pneumonia was assessed using a multivariate logistic regression analysis controlling for illness severity (acute and chronic). In the prospective cohort study,[70] the rate of unrecognized misplaced ETT was compared between patients who had $ETCO_2$ monitoring and those who did not. The statistical test performed was unclear.

Study Funding

No funding source was disclosed for one study.[69] The other study stated that one study author was a consultant for the capnography manufacturer (Oridion).[70]

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Two randomized[71,72] and one non-randomized[73] study met the inclusion criteria of the clinical review for pediatric patients in serious or critical condition (Table 1). One study enrolled infants who required mechanical ventilation in the delivery room or in the neonatal ICU,[72] and two studies included infants who were preterm (< 32 weeks[73] or < 34 weeks gestation[71]) or were at high risk of needing resuscitation and receiving ventilation.[71] Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication

The studies were published in 2015[72,73] and 2013[71] and took place in Ireland,[73] Israel,[72] and the US.[71]

Study Setting

The studies were conducted in a university maternity hospital,[73] the labour and delivery unit of a medical centre,[71] and the neonatal ICU of a university-affiliated tertiary care centre.[72]

Study Size

Sample sizes were 92 in the non-randomized study,[73] and 50[71] and 66[72] in the randomized studies.

Study Design

In Kong 2013,[71] infants in the intervention group were monitored with capnography and the resuscitation team was told to keep $ETCO_2$ levels between 40 mm Hg and 55 mm Hg. In the control group, the $ETCO_2$ monitor display was covered and the resuscitation team was told to adjust ventilation as required according to their clinical judgment. The treatment team in the other RCT used the capnography data to guide patient care; however, no target $ETCO_2$ level was prescribed. In the control group, the $ETCO_2$ data were covered, but the capnography tracing was visible to the treatment team to ensure adequate measurements and to indicate when a change to the sampling line was required.[72] In the prospective cohort study,[73] all infants in the intervention group were monitored with capnography as soon as they were placed on the resuscitation table. The treatment team was told to obtain capnography waveforms but not to change patient management based on the numeric (capnometry) values. The comparator group was a historical cohort that was not monitored with capnography.[73]

Intervention

The capnography devices used for $ETCO_2$ monitoring in the included studies were one of the following:

- NICO Respiratory Profile Monitor[71]
- Philips Intellivue monitor[73]

- Capnostream 20p.[72]

The NICO respiratory profile monitor was a mainstream, multi-parameter model that used a PediCap device to detect carbon dioxide levels. The remaining two devices were sidestream, portable, and multi-parameter models (measuring two or more of parameters such as $ETCO_2$, SpO_2 and respiratory rate) and was connected to the patient via a sampling line. A detailed description of the capnography devices used in the included studies can be found in APPENDIX 8: Details of the Capnography Devices.

Comparators

Randomized Studies

In one RCT,[71] full details of the monitoring available for patients in the comparator group were unknown; however, pulse oximeters were used for all patients, and it was stated that ventilation was provided based on clinical assessment of patients in the control group.[71]

Non-randomized Studies

No information was provided to describe what comprised standard monitoring for patients in the historical control group in Hawkes 2015[73] or the masked control group in Kugelman 2015.[72]

Outcomes Measured

In the two randomized studies, the primary outcome was related to whether a patient was within a target range for PCO_2. In one study, the primary outcome was measured as the number of patients within a PCO_2 range of 40 mm Hg to 60 mm Hg upon admission to the ICU (approximately one hour after birth)[71] and, in the other study, it was measured as the percentage of time spent in a safe PCO_2 range of 30 mm Hg to < 60 mm Hg.[72] Secondary outcomes were not explicitly identified in one study,[72] but the other study included duration of ventilation and adjustment of ventilation variables.[71] Other outcomes measured in Kugelman[72] included the number of arterial blood gas measurements, the number of chest radiographs, duration of mechanical ventilation, and length of stay.[72] In the non-randomized study, the outcomes measured included the number of patients intubated and the percentage of patients within the target PCO_2 range (5 kPa to 8 kPa).[73]

Statistical Analysis Plan

In the randomized studies, the primary outcome was assessed using the chi-squared test,[71] and an unpaired two-sample t test.[72] In Hawkes 2015,[73] the percentage of patients within the PCO_2 target range was compared between the capnography group and the historical control group using Fisher's exact test.[73]

Study Funding

Manufacturers provided the devices and sampling lines in one study.[72] A foundation research award and fellowship supported the prospective cohort study.[73] No funding source was reported in one study and the authors stated there were no conflicts of interest.[71]

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

Two studies (one randomized study[32] and one prospective cohort study[74]) met the inclusion criteria of the clinical review for adult patients being monitored in a post-operative setting (Table 1). Details of the study characteristics are provided subsequently and in APPENDIX 7: Detailed Study Characteristics.

Country and Year of Publication
The studies were published in 2008[32] and 2013,[74] and both were conducted in the US.

Study Setting
Both studies took place in a hospital post-anesthesia care unit, one of which was an academic tertiary care facility.[74]

Study Size
Fifty-four patients were included in the randomized study,[32] and 33 patients were included in the prospective cohort study.[74]

Study Design
Hutchison 2008[32] randomized patients to either the intervention group, which included all patients being continuously monitored with capnography, or a control group where patients were monitored every four hours by observation or auscultation using pulse oximetry and respiratory rate. In Ramsay 2013,[74] all patients in the retrospective cohort were monitored with RAM and capnography, and the resulting data were retrospectively reviewed and compared with manually annotated data. The reference method (manual annotation) consisted of the use of the acoustic and capnography data (as well as breathing sounds) annotated by a trained technician.

Intervention
The capnography devices used for $ETCO_2$ monitoring in the included studies were one of the following:

- Capnostream 20[74]
- Alaris $ETCO_2$ module.[32]

Both devices are mainstream, multi-parameter models (measuring two or more of parameters such as $ETCO_2$, SpO_2, respiratory rate and fraction of inspired oxygen), connected to the patient via a nasal cannula[32] or a Smart CapnoLine.[74] The Capnostream is a portable stand-alone device, while the Alaris $ETCO_2$ module is an add-on to the Alaris monitoring system. A detailed description of the capnography devices used in the included studies can be found in APPENDIX 8: Details of the Capnography Devices.

Comparators
Randomized Studies
Full details of the monitoring available for the comparator group are unknown; however, pulse oximetry and respiration rate (by observation and auscultation) were monitored.[32]

Non-randomized Studies
The comparator device in Ramsay 2013[74] was a pulse CO-Oximeter with RAM technology. Respiratory rate was measured using a bioacoustics sensor applied to the patient's neck.[74]

Outcomes Measured
In the randomized study,[32] the primary outcome was respiratory depression, and secondary outcomes included pauses in breathing during sleep, time in the post-anesthesia care unit, and morphine consumed.[32] In the non-randomized study,[74] primary and secondary outcomes were not explicitly identified as such; however, measured outcomes included respiratory pause and the percentage of time the device provided data.[74]

Statistical Analysis Plan
In the randomized study,[32] no formal statistical analyses were conducted for the outcomes of interest for this review. In the non-randomized study,[74] the comparative effectiveness of the devices with respect to their sensitivity in detecting a respiratory pause was assessed statistically using Fisher's exact test.

Study Funding
In one study, funding for the research personnel who collected the study data and provided the equipment was provided by the device manufacturer.[74] The authors of this study also received manufacturer funding, and one author was employed by the company.[74] In the other study, the manufacturer supplied the devices, and provided an honorarium to one of the study authors for speaking at a convention.[32]

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care
No studies of pediatric patients being monitored in a post-operative setting met the inclusion criteria for the clinical review (Table 1).

4.2.3 Patient Characteristics
Details of the patient characteristics for each research question are summarized below. Additional detail can be found in APPENDIX 9: Detailed Patient Characteristics.

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation
Seventeen (seven randomized[19,20,38,48,51,54,61] and 10 non-randomized[50,52,53,55-60,62]) studies included adult patients undergoing procedural sedation. The mean and median ages of the participants in the included studies were primarily older than 50 years[20,38,50,52,54,56,59,60,62,75] and ranged from 24 years[61] (patients were primarily undergoing surgical abortion) to 62.5 years[59] (patients were all undergoing percutaneous transhepatic cholangiodrainage). Two of the studies included both adult and pediatric patients,[57,58] but are included in this review for the adult population because the majority of patients were adults (median age 38 years;[58] 85% adult[57]). Two studies[53,61] included only female patients, and the others had populations that ranged from 25%[56] to 90%[60] male, with the majority of the studies having populations between 40% and 60% male.[19,20,38,50-52,54,55,57-59,62,75]

Mean BMI was reported in the majority of included studies[20,38,51-54,56,59,61,75] and ranged from just over 23 kg/m^2 to 31.6 kg/m^2.[56,61] Smoking status and comorbid conditions were poorly reported. A minority of studies reported smoking status,[20,38,51,52,54,59,62] or more than one comorbid condition.[20,38,52,59,62] The percentage of current or former smokers ranged from 10%[52] to 47%,[51] and the percentage of patients with cardiovascular or heart disease ranged from 16%[62] to 38%.[20]

The type of procedure for which patients were being sedated was not reported in one study,[53] and was reported in general terms (orthopedic, vascular, pain, and gastroenterology procedures) in one study.[50] In the remaining studies, patients underwent the following procedures, with some studies including patients undergoing one of several possible procedure types:

- fracture reduction or joint reduction (N = 5)[6,19,55,57,58]
- colonoscopy (N = 4)[20,38,52,62]
- upper or lower endoscopy (N = 3)[48,54,60]
- abscess and incision drainage(N = 3)[19,55,57]

- endoscopic retrograde cholangiopancreatography (N = 2)[51,54]
- surgical abortion (N = 1)[61]
- knee replacement (N = 1)[56]
- percutaneous transhepatic cholangiodrainage (N = 1).[59]

Two studies did not report the type or dose of sedative used.[53,56] One study reported that patients received a combination of midazolam, propofol, and fentanyl.[50] In the remaining studies, patients received one of several possible types of sedatives, including:

- propofol (N = 9) [19,20,38,48,55,58,59,61,62]
- propofol with alfentanil (N = 1)[61]
- propofol with midazolam and/or ketamine (N = 1)[20]
- propofol with midazolam (N = 1)[51]
- propofol with fentanyl and midazolam (N = 1)[62]
- midazolam with meperidine or fentanyl (N = 3)[52,54,57]
- midazolam (N = 3)[58-60]
- pentazocine (N = 1)[60]
- pethidine with midazolam (N = 1)[62]
- etomidate (N = 1)[58]
- ketamine (N = 1).[58]

Procedure lengths varied from less than 20 minutes[19,61] to 174 minutes.[60] Eight studies did not report the length of the procedures[50,52,53,55-59] and, of those reported, the procedure length generally lasted between 20 and 40 minutes.[20,38,48,51,54,62] In most studies, the provision of supplemental oxygen was part of routine care during the procedures.[19,20,38,48,50,51,53,56,58-60,62]

The depth of sedation was generally poorly reported, with five studies reporting a mean or median Ramsay sedation score of ≥ 4,[19,53,55,57,61] and one reporting the percentage of patients who were under "deep sedation" (92% in the intervention group and 94% in the comparator group; defined as the patient being unable to respond to verbal commands or to react to endoscopic maneuvers).[20] Most studies reported an ASA class for the participating patients and, of those studies, two included patients of an ASA class greater than III (Schlag 2013[59] one patient with ASA class IV, and Klare 2016[51] with 10 patients with ASA class IV).[20,38,48,52,54,59-62] An ASA score of I to III indicates that patients were either healthy or had non-life-threatening mild or severe systemic disease prior to their procedure.[76]

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Four (two randomized[65,68] and two non-randomized[66,67]) studies included pediatric patients undergoing procedural sedation. Three studies had a mean or median age of 10 years or older,[66,68,77] and one study had a median age just over 14 years old.[65] One study did not report the percentage of male or female patients,[66] and the remaining three populations were more than 50% male.[65,67,68] BMI and comorbid conditions were not reported in any of the four studies. The studies included patients undergoing the following procedures, with some studies including patients undergoing one of several possible procedure types:

- fracture reduction (N = 2)[66,68]
- endoscopy (N = 1)[65]
- colonoscopy (N = 1)[65]
- joint reduction (N = 1)[66]
- laceration repair (N = 1)[68]

- incision and drainage of abscess (N = 1)[68]
- brain MRI (N = 1).[67]

The following types of sedative were used during the procedures, with some study protocols including a range of sedatives:
- midazolam (N = 3)[65,67,68]
- fentanyl (N = 2)[65,67]
- ketamine (N = 1)[68]
- phenobarbital (N = 1)[67]
- chloral hydrate (N = 1)[67]
- propofol (N = 1).[66]

Procedure length was not reported in the two non-randomized studies[66,67] of the two RCTs; mean procedure length was 10 minutes (patients who underwent endoscopy) in one study,[65] and a mean of 39 minutes (patients receiving colonoscopy) in the other study.[65] Routine administration of supplemental oxygen occurred in one study.[65]

Depth of sedation was reported in two of the studies.[65,66] Ramsay sedation scores ranged between 2 and 4 in Lightdale 2006,[65] and the median Ramsay sedation score was 6 (range 3 to 8) in Anderson 2007.[66] Three studies included patients with an ASA score of I or II,[65-67] indicating patients were either healthy or had mild systemic disease, and one study included patients with an ASA score of I, II, or III, indicating that patients were included even if they had non–life-threatening severe systemic disease (ASA class III).[68,76]

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

One included study examined adult patients requiring CPR.[1] This study examined 1,113 patients (53 in the $ETCO_2$ group and 1,060 in the propensity-matched cohort; 50.9% male in the $ETCO_2$ group and 60.8% male in the matched cohort) with a mean age of 68 years or older in both groups.[1] Approximately 71% of patients in each group had some form of cardiovascular disease, and CPR was performed for a mean of 25 minutes in the $ETCO_2$ group and a mean of 27 minutes in the control group.[1]

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No studies met the inclusion criteria of the clinical review for pediatric patients undergoing CPR.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition

The retrospective study examining adults in serious or critical condition reported limited details on the patient characteristics.[69] The prospective study that included adult and pediatric patients in serious or critical condition primarily consisted of adults; however, the exact number of pediatric patients was not explicitly stated in the study report. The mean age of patients was older than 40 years.[70] Most were male (69.9%) trauma patients (78%) and all patients were intubated.

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Two randomized[71,72] and one non-randomized[73] study examining pediatric patients in serious or critical condition were included. All studies included preterm infants (mean or median gestational age < 30 weeks in all studies) and two of the studies (the Kong RCT[71] and the

Hawkes non-randomized study[73]) consisted of at least 60% male infants (the Kugleman RCT[72] did not report the sex of the study infants). The sample sizes were 50[71] and 66[72] in the two RCTs, and 92[73] in the non-randomized study. The minority of infants were intubated in the non-randomized study[73] (< 32%), 52% of the infants were intubated in the Kong RCT,[71] and all patients were intubated in the Kugelman study.[72]

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

One randomized[32] and one non-randomized study[74] examining adult patients receiving care in the post-operative setting were included. The procedures performed were orthopedic (i.e., knee and hip replacement, shoulder repair) in the randomized study[32] and primarily gastrointestinal surgeries, including gastric bypass or gastric sleeve, in the non-randomized study.[74] The mean age of patients in the randomized study[32] was older than 60 years and in the non-randomized study[74] was a mean of 45 years. Mean BMI was < 35 kg/m^2,[32] and > 40 kg/m^2.[74] Sleep apnea was an exclusion criteria in the randomized study[32] and at least 40% of patients in the non-randomized study had sleep apnea.[74] Almost all of the patients in both studies (100%[32] and 97%,[74] respectively) were prescribed post-operative pain medication.[32,74]

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

No studies met the inclusion criteria of the clinical review.

4.2.4 Quality Assessment and Risk of Bias Assessment

Details of the quality assessment and risk of bias assessment for each research question are summarized below. Additional detail for each study can be found in APPENDIX 10: Detailed Tables for Risk of Bias Assessment.

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

All RCTs had adequate sequence generation and allocation concealment, except for two studies[51,61] where there was insufficient information to judge the adequacy of allocation concealment in one, and sealed envelops were not stated as being opaque in another.[51] Due to the nature of the intervention, blinding of the treatment team and outcome assessors was not possible in most cases, except for Qadeer[54] where the treatment team was blind to patient allocation, and Deitch 2010,[19] where the study investigators assessed each graph for the outcomes measured (i.e., hypoxia and respiratory depression) prior to study blinding being broken. In two studies, patients were excluded if they had missing data,[48] or had > 35% missing data,[19] so any potential differential in missing data between the intervention and control groups is unknown. In the remaining studies, the reasons for attrition were described[20,38,51,54,61] and were minimal, with no apparent differential between study groups. The risk of selective reporting was minimal among the studies with a clinicaltrials.gov record,[20,38,48,51,54,61] as the outcomes listed in the registry were aligned with the outcomes reported in the articles. One study reported material support being provided to study authors from the manufacturer for research purposes.[51] Other concerns related to study quality include the potential for two studies being underpowered[19,61] and, in one study,[38] baseline differences in patient characteristics between groups suggesting potential problems with randomization, despite adequate randomization and concealment (the baseline differences between groups were adjusted for in the analysis).[38]

All prospective cohort studies included patients who were monitored by both capnography and the comparator, so the potential bias associated with the differential selection of patients between an intervention and control group is not applicable in these studies. In the prospective cohort study where patient outcomes were compared before and after implementation of $ETCO_2$, there was evidence of differences in baseline characteristics between the $ETCO_2$ group and the no-$ETCO_2$ group on factors that may influence outcomes. In the prospective cohort studies, study investigators who were responsible for recording patient data during the procedure (i.e., $ETCO_2$, SpO_2, clinical observations) were not blinded to each monitoring modality; therefore, it is possible that the interpretation of one set of monitoring data could influence the interpretation of another set — particularly for subjective outcomes — potentially resulting in a decreased likelihood of finding a difference between the methods of monitoring within a given study. There was no indication of selective reporting in one study that had a protocol available,[53] and the extent of selective reporting in the remaining studies is unknown. Furthermore, primary and secondary outcomes were not explicitly stated in all studies, except one.[59] The number of patients who were approached for the study and subsequently accepted and enrolled was poorly reported in all studies except De Oliveira 2010, where all but one individual agreed to participate.[53] Studies reported either minimal or no patients being lost to follow-up;[50,53,55-59] otherwise, there was no mention of whether or not missing data were present.[52,60,62] All studies except two,[52,62] demonstrated an acceptable effort to minimize bias (i.e., most checklist criteria were met). In one study,[62] study methodology was inadequately reported to comment on the extent to which biases were or could have been minimized. In the other study,[52] the imbalance in baseline characteristics between the intervention and control groups is particularly concerning. In addition, the nature of changes that occurred from before the implementation of capnography to after, and how these changes may have influenced the results, was not fully explored. Some design features of the studies made them particularly susceptible to biases: Schlag 2013[59] was not intended to be an interventional study, three studies were not designed to assess the effectiveness of $ETCO_2$ monitoring,[50,55,57] Burton 2006[58] was terminated prematurely based on an interim safety analysis, and Tanaka 2014[56] was classified as a pilot study with 20 patients enrolled.

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

The two RCTs had adequate sequence generation and allocation concealment. Given the nature of the study design, patients and physicians were blinded to patient treatment group in Lightdale 2006 (physicians were signalled by an independent investigator if hypoventilation was detected by the capnography device for > 15 seconds in the intervention group and > 60 seconds in the control group), [65] but blinding was not possible in Langhan 2015,[68] where capnography was either visible or not visible to the treatment team. Outcome assessors were not blinded to patient allocation in either study. Other potential concerns about study quality include an outdated pulse oximetry device in one study,[65] and the potential for inadequate power in the other study.[68]

In the two prospective cohort studies, all patients were monitored by both capnography (i.e., the intervention) and standard monitoring (i.e., the comparator), so the potential bias associated with the differential selection of patients between an intervention and control group is not applicable in these studies. However, both studies recruited patients based on a convenience sample limited to the availability of the research assistant, so selection bias is a concern. Selection bias may be particularly problematic in Kannikeswaran 2011[67] where patients were excluded from the study due to $ETCO_2$ device malfunction (n = 10; 5%) or nasal cannula dislodgement (n = 12; 6%). This exclusion may lead to results in favour of the capnography because these intervention failures are not considered in the analysis. In both studies, the

research assistants who were responsible for recording patient data (i.e., $ETCO_2$, airway events and interventions) during the procedure were not blinded to each monitoring modality. It is possible that the interpretation of one set of monitoring data would influence the interpretation of another set, particularly for subjective outcomes (for example, adverse or acute airway events defined by clinical observation criteria), potentially resulting in a decreased likelihood of finding a difference between the methods of monitoring within a given study. Study methodology was not described in detail in Anderson 2007;[66] it is uncertain if the treating team could see the $ETCO_2$ readings.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

The retrospective cohort study[1] included patients from an insurance claims database who were classified as having (or not having) received $ETCO_2$. Patients in the intervention and the control groups were selected from the same cohort of patients, with the control group being selected based on propensity score matching with the intervention group. Patients were selected as having an out-of-hospital cardiac arrest based on international classification of diseases (ICD) codes for ventricular fibrillation, cardiac arrest, and sudden death. The authors do not present a comparison of the number of cases for each indication (by ICD code) between cases and controls. It is possible there were differences in the proportion of patients with each indication between cases and controls and, therefore, a systematic difference between the rate of exposure and outcome between the two groups. The authors recognize that the measurement of exposure status (i.e., the use of $ETCO_2$) may not have been recorded and billed in all cases. The presence of incorrect classification of exposure status is likely to bias the result in the direction of no effect. Hospital admission was used as a surrogate for ROSC and, due to the reliance on clinical records, survival to hospital discharge was known only if it was recorded in the patient's chart. The study authors did not discuss the validity of these assumptions, and it is unclear if there would be a relationship between the documentation of these outcomes and a patient's exposure status.

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No studies met the inclusion criteria of the clinical review for assessing capnography for pediatric patients undergoing CPR.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition

Two studies had key limitations that made it difficult to suggest a clear association between the use of capnography and the outcomes measured (i.e., mortality and ventilator-associated pneumonia,[69] and unrecognized misplaced ETT[70]). In the retrospective chart review,[69] there was a limited number of patients who were monitored with capnography (5.9%; N = 169) suggesting an underpowered study, and the authors made no conclusions specific to the value of capnography monitoring. In Silvestri 2005,[70] patients were assessed for the primary outcome (i.e., rate of unrecognized misplaced ETT) upon enrolment. Exposure status was subject to recall bias as it was retrospectively assessed using self-reporting by the treatment team, and may have been influenced by knowledge of the primary outcome. One author in this study was noted to be a consultant for the capnography manufacturer.[70]

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Selection bias was minimized in two studies with appropriate randomization and allocation concealment in Kong 2013,[71] and the selection of a historical control group with similar

characteristics in Hawkes 2015.[73] It is unclear in Kong 2013[71] who was responsible for recording study outcome data and if they were blind to patient allocation. Similarly, the type of standard monitoring equipment used by clinicians in the historical cohort in Hawkes 2015[73] is unknown. Hawkes 2015[73] was also not designed to assess the impact of $ETCO_2$ monitoring on patient outcomes and, therefore, may have been inadequately powered with limited data on potential confounders.

There were several key methodological concerns in Kugleman 2015.[72] The method of randomization and allocation was unclear, patients and the treatment team were not blind to patient allocation, and it is unclear who was responsible for measuring the primary outcome and whether they were blind to patient allocation. Additionally, there was an imbalance in the number of patients with missing data due to technical problems between the groups (6/25 [24%] in the intervention group; 2/30 [7%] in the control group), and the results for the primary outcome were not reported. The greater number of patients with missing data in the intervention group may bias the results in favour of the capnography group because these intervention failures are not considered in the analysis. There was insufficient reporting of study methods to adequately assess the direction of the remaining biases. It should also be noted that one study author was employed by the manufacturer of the capnography device used in the study.[72]

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

Hutchison 2008[32] was particularly limited by lack of reporting of several methodological criteria for assessing risk of bias, including their randomization procedure, efforts for allocation concealment, blinding, and the existence and handling of missing data. Additionally, the results of the study indicate that all respiratory events were detected by respiratory-rate changes or apnea detection, and not by pulse oximetry or capnography, suggesting there may be something else other than the devices that are detecting events differentially between the groups. Ramsay 2013[74] included a cohort of patients who were monitored by both capnography and RAM, so the potential bias associated with the differential selection of patients between an intervention and control group is not applicable for this study. The detection of a respiratory event was based on a comparison to a reference that was evaluated by a trained technician and confirmed by a second technician. Despite this, it is possible that the number of events is overstated because the reference was based on respiratory pauses that were detected by capnography and RAM, and not on an independent measure. Both studies noted author affiliations with industry (a speaking honorarium in one study,[32] and funding and employment in the other).

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

No studies met the inclusion criteria of the clinical review for assessing capnography for pediatric patients being monitored in a post-operative care setting.

4.2.5 Data Analysis and Synthesis

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

Primary Clinical Effectiveness Outcome

Detection of Respiratory Failure: Hypoxemia

Capnography Versus Standard Monitoring: A measure of hypoxemia was reported in seven RCTs[19,20,38,48,51,54,61] and two non-randomized studies.[52,59] The pooled analysis only included

outcomes reported in the RCTs. The two non-randomized studies were prospective studies, one of which was a non-interventional study that measured the number of hypoxemia events predicted by capnography versus those predicted by clinical observation,[59] and the other was a prospective cohort study that assessed sedation events (including O_2 saturation < 90%, or requiring intervention) in patients seen before and after the implementation of capnography.[52] These two studies were deemed inappropriate to pool with the interventional RCTs due to differences in study designs,[59] methodological concerns,[52] and poor reporting of outcomes and results.[52] The pooled results found a statistically significant reduced risk of detecting hypoxemia (SpO_2 < 93% to SpO_2 < 90%) in the intervention group (capnography with standard monitoring) versus the comparator group (standard monitoring alone). The risk of detecting hypoxemia was approximately one-third less likely (RR 0.70; 95% CI, 0.59 to 0.83) in the intervention group versus the comparator group (Table 2). The I^2 measure for heterogeneity was 43%, indicating there may be moderate heterogeneity between studies.[49] The clinical characteristics (i.e., different procedure types, sedation levels, length of procedure, and patient characteristics such as BMI, smoking status and comorbid conditions) and methodological characteristics (i.e., type of comparator, the clinician performing the sedation, definition of hypoxemia, and how patients with missing data were handled) of the included studies were actively explored as likely sources of the heterogeneity found in this analysis. Individual study data and the forest plot can be found in Table 55 and Figure 5, respectively (APPENDIX 11: Detailed Outcome Results — Clinical Review).

Two sensitivity analyses were performed to assess the robustness of findings to the inclusion of studies with different characteristics:

1. Excluding van Loon 2014,[61] due to differences in patient characteristics (all female, young, and otherwise healthy patients) resulting from the type of procedure performed (i.e., surgical abortion).
2. Excluding Qadeer 2009[54] due to differences in sedative type used (i.e., patients were sedated with midazolam and meperidine or fentanyl).

A statistically significant reduced risk of detecting hypoxemia was maintained in the intervention group versus the comparator group when van Loon 2014[61] was excluded from the analysis, although the RR is lower than in the main analysis (RR 0.66; 95% CI, 0.58 to 0.75; I^2 = 0%) (Table 2). A statistically significant reduced risk of detecting hypoxemia, approximately the same order of magnitude, was also maintained in the intervention group versus the comparator group when Qadeer 2009[54] was excluded from the analysis (RR 0.71; 95% CI, 0.57 to 0.89; I^2 = 51%) (Table 2).

Table 2: Pooled Analysis for the Detection of Respiratory Failure (Hypoxemia) for Adults Undergoing Procedural Sedation (RCTs, Random Effects Model)

Hypoxemia (SpO_2 < 93% to SpO_2 < 90%)	Standard Monitoring + Capnography		Standard Monitoring		Effect Estimate and Measure of Heterogeneity			
	Events	Total	Events	Total	RR	95% CI		I^2
Primary analysis (Total number of patients = 2,862)								
Randomized studies (n = 7)	285	1,432	404	1,430	0.70	0.59	0.83	43%
Sensitivity analyses								
Excluding van Loon 2014[61] (n = 6)[a]	232	1,226	352	1,221	0.66	0.58	0.75	0%
Excluding Qadeer 2009[54] (n = 6)[b]	228	1,308	319	1,307	0.71	0.57	0.89	51%

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SpO_2 = arterial oxygen saturation measured with pulse oximetry.
[a] Limited to studies with patients undergoing clinically similar procedures.
[b] Limited to studies that use propofol alone, or propofol in combination with other drugs for sedation.

Detection of Respiratory Failure: Severe Hypoxemia

Capnography Versus Standard Monitoring: A measure of severe hypoxemia (SpO_2 < 88% to SpO_2 < 81%) was reported in six of the seven RCTs,[20,38,48,54,61,78] and in none of the prospective cohort studies.[53,55-60,62] The pooled analysis included outcomes reported in the RCTs. There was a lower risk of detecting severe hypoxemia in the intervention group (capnography with standard monitoring) versus the comparator group (standard monitoring alone) (RR 0.73; 95% CI, 0.54 to 0.98); however, this result was only borderline statistically significant. There was evidence for moderate heterogeneity between studies (Chi^2 = 8.42, degrees of freedom [df] = 5, *P* = 0.13; I^2 = 41%).[49] (Table 3). In addition to the likely sources of heterogeneity described earlier for hypoxemia, there were also fewer studies and a wider variation in the definition of severe hypoxemia for this analysis compared with the measure of hypoxemia. Detailed outcome data and a forest plot can be found in Table 55 and Figure 6, respectively (APPENDIX 11: Detailed Outcome Results — Clinical Review). Two sensitivity analyses were performed to assess the robustness of findings:

1. Excluding van Loon 2014[61] due to differences in patient characteristics (all female, young, and otherwise healthy patients) resulting from the type of procedure performed (i.e., surgical abortion).
2. Excluding Qadeer 2009[54] due to differences in sedative type used (i.e., patients were sedated with midazolam and meperidine or fentanyl).

A statistically significant reduced risk of detecting severe hypoxemia was maintained between the intervention group and the comparator group when van Loon 2014[61] was excluded from the analysis, although the RR was slightly lower than in the main analysis (RR 0.70; 95% CI, 0.51 to 0.97, I^2 = 48%)(Table 3). In contrast, when Qadeer 2009[54] was excluded from the analysis, there was a non-statistically significant difference in the risk of detecting severe hypoxemia between the intervention group and the comparator group; the RR of detecting severe hypoxemia was higher than in the main analysis (RR 0.80; 95% CI, 0.59 to 1.09, I^2 = 43%) (Table 3).

Table 3: Pooled Analysis for the Detection of Respiratory Failure (Severe Hypoxemia) for Adults Undergoing Procedural Sedation (Randomized Studies Only, Random Effects Model)

Severe Hypoxemia (SpO_2 < 88% to SpO_2 < 81%)	Standard Monitoring + Capnography		Standard Monitoring		Effect Estimate and Measure of Heterogeneity			
	Events	Total	Events	Total	RR	95% CI		I^2
Primary analysis (total number of patients = 2,845)								
Randomized studies (n = 6)	115	1,364	158	1,366	0.73	0.54	0.98	41%
Sensitivity analyses								
Excluding van Loon 2014[61] (n = 5)[a]	108	1,158	152	1,157	0.70	0.51	0.97	48%
Excluding Qadeer 2009[54] (n = 5)[b]	96	1,240	120	1,243	0.80	0.59	1.09	25%

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SpO_2 = arterial oxygen saturation measured with pulse oximetry.
[a] Limited to studies with patients undergoing clinically similar procedures.
[b] Limited to studies that use propofol alone, or propofol in combination with other drugs for sedation.

Detection of Respiratory Failure: All Reported SpO_2 Measures

Capnography Versus Standard Monitoring: All other study-specific measures of SpO_2 that were not included in the pooled analyses are included in Table 56 (APPENDIX 11: Detailed Outcome Results — Clinical Review). Four RCTs[38,48,51,61] and two prospective cohort studies[52,59] reported additional measures of oxygen desaturation that were not included in the pooled analysis or did not fall within the definitions of hypoxemia and severe hypoxemia that were used for the pooled analysis. Among the randomized studies, there were no statistically significant differences in the remaining SpO_2 outcomes between groups, except in Beitz 2012[38] where a statically significantly greater number of oxygen-desaturation events were detected in the comparator group compared with the intervention group ($P < 0.001$). Among the prospective cohort studies, one study reported outcomes measured by pulse oximetry,[59] and the other study reported oxygen saturation (but it is unclear how it was measured). In Schlag 2013,[59] hypoxemia was detected in three patients; each of the three cases were predicted by capnography and one of the three was predicted clinically ($P = 0.22$). Likewise, a greater number of oxygen-desaturation events were predicted by capnography compared with clinical observation (n = 10; 80% versus 20%, respectively). In the prospective cohort that assessed outcomes in patients before and after implementation of $ETCO_2$ monitoring, the unadjusted analyses found that a higher percentage of patients in the $ETCO_2$ group experienced a sedation event (O_2 saturation < 90% or requiring intervention) compared with the no-$ETCO_2$ group (5% versus 2.4%; $P = 0.04$).[52] However, this analysis did not control for potential confounding variables; the results of the multivariate analysis were not reported for this outcome.[52]

Overall, there was a lower likelihood of hypoxemia when patients were monitored with capnography. These results were statistically significant for hypoxemia and numerically lower for severe hypoxemia, and were most often lower for other measures of SpO_2. One observational study reported greater ability to predict the occurrence of hypoxemia with the use of capnography.

Other Clinical-Effectiveness Outcomes

Detection of a Respiratory Event

Capnography Versus Standard Monitoring: Among the randomized studies, five studies reported an outcome related to a respiratory event (Table 57).[19,20,38,51,54] The definition of a respiratory event was inconsistent between studies. In four studies,[19,20,38,51] a respiratory event (as indicated by apnea, altered ventilation, and respiratory depression), was defined by $ETCO_2$ and waveform criteria. There was no comparative evidence available in one study.[20] In Beitz 2012[38] and Klare 2016,[51] there was a statistically significantly greater proportion of patients for which apnea or altered ventilation was detected in the intervention group versus the comparator group (56.7% versus 2.1%, and 64.5% versus 6.0%, respectively; $P < 0.001$ in both cases). In Deitch 2010,[19] there were approximately an equal number of events detected in the intervention and comparator groups (57% versus 58%, respectively). In the fifth study, Qadeer 2009,[54] the definition of abnormal ventilation was the same as the criteria that were used to signal to the treatment team that the patient was not breathing properly (i.e., a flat waveform for > 5 seconds, a > 75% reduction in waveform amplitude compared with baseline, or a respiratory rate of < 8 breaths/minute). There were no statistically significant differences between the intervention and comparator groups for the number of patients experiencing abnormal ventilation (77% versus 82%; $P = 0.29$). Apnea was a more progressed version of abnormal ventilation (defined by a flat capnographic waveform ≥ 15 seconds). There was a statistically significantly lower proportion of patients experiencing an apnea event in the intervention group versus the comparator group (63% versus 41%; $P < 0.001$).[54]

Among the 10 prospective cohort studies, six studies reported an outcome related to a respiratory event (Table 57).[50,55,57-59,62] There was no comparative evidence available in Cacho 2010.[62] In Schlag 2013,[59] 20 patients experienced apnea, among whom there was a statistically significantly greater proportion of patients detected as having apnea with capnography data compared with those detected by clinical observation (80% versus 30%, respectively; $P = 0.001$). Likewise, in Deitch 2008,[55] the proportion of patients with recognized respiratory depression by capnography data was numerically greater in the intervention group compared with the comparator group, but only for those patients in the supplemental oxygen group (77% versus 37%), and not the room air group (59% versus 59%); no statistical testing was conducted. In Deitch 2007,[57] the proportion of patients with recognized respiratory depression by capnography data was greater in the intervention group compared with the comparator group for those patients in the supplemental oxygen group (95% versus 15%), and in the room air group (84% versus 26%); no statistical testing was conducted. Burton 2006,[58] reported 20 acute respiratory events detected by pulse oximetry and clinical observation from 60 encounters with 59 patients. Of these 20 acute respiratory events, 17 were detected by capnography data, and 14 of the 17 events were detected by $ETCO_2$ data prior to standard monitoring. In Soto 2005,[50] all episodes of apnea were detected by capnography, and none were detected by standard monitoring. Additionally, similar to the results of Burton 2006,[58] a greater percentage of patients who experienced oxygen saturation < 90% had a preceding apnea event detected by capnography (55% [11/20]); versus 30% (6/20) apnea detection after oxygen desaturation.

Where comparative evidence was available, the ability to detect a respiratory event was generally favoured with the use of capnography compared with standard monitoring. Evidence from two studies suggested that capnography may be of particular benefit for monitoring patients who are receiving supplemental oxygen compared with room air.

Capnography Versus Rainbow Acoustic Monitoring: One study compared the effectiveness of capnography versus RAM and clinical observation for detecting a respiratory pause (Table 58).[56] A greater proportion of patients were identified as having a respiratory pause

based on capnography data compared with RAM data and clinical observation (88% versus 55% versus 16%, respectively); no statistical testing was conducted.[56]

Capnography Versus Transcutaneous Capnography: Two studies compared the effectiveness of capnography versus transcutaneous capnography for detecting hypoventilation (Table 59).[53,60] In De Oliveira 2010,[53] a smaller proportion of patients were identified as having hypoventilation based on capnography data compared with transcutaneous capnography data (1/12 [8.3%] versus 12/12 [100%]); this result was not statistically significant (P = 0.09).[53] In Kusunoki 2012,[60] there were 12 events of SpO_2 < 90%; in 10 (83%) of these cases, $ETCO_2$ capnography detected a decrease in respiratory rate prior to the event. Transcutaneous capnography did not provide any indication of the observed events prior to their occurrence.

Time to Detection of a Respiratory Event
For the time to detection of a respiratory event, no studies assessed the effectiveness of capnography compared with other forms of monitoring.

Change in Clinical Management
Capnography Versus Standard Monitoring: There were one or more outcomes reported for change in clinical management in all seven randomized studies,[19,20,38,48,51,54,61] and in four of the prospective cohort studies.[52,57,58,62] Pooled analysis was possible for the six randomized studies that reported the number of patients who required changes to supplemental oxygen,[20,38,48,51,54,61] and for the four randomized studies that reported the number of patients who required ventilation support.[20,38,48,51] There were no statistically significant differences between the intervention group (capnography with standard monitoring) versus the comparator group (standard monitoring) for the need for supplemental oxygen (RR 0.92; 95% CI, 0.75 to 1.12) (Table 4). There was evidence for moderate heterogeneity between studies (Chi2 = 8.92, df = 5, P = 0.11; I2 = 44%).[49] Differences in study design, the threshold for clinical intervention between centres and physicians, and patient characteristics (procedures performed, depth of sedation, and duration of procedure) were actively explored as possible sources of heterogeneity for this analysis. Individual study data and a forest plot can be found in Table 60 and Figure 7, respectively (APPENDIX 11: Detailed Outcome Results — Clinical Review).

Table 4: Pooled Analysis for Change in Clinical Management (Supplemental Oxygen) for Adults Undergoing Procedural Sedation (Randomized Studies, Random Effects Model)

Change in Clinical Management (*Supplemental Oxygen*)	Standard Monitoring + Capnography		Standard Monitoring		Effect Estimate and Measure of Heterogeneity			
	Events	Total	Events	Total	RR	95% CI		I^2
Primary analysis (Total number of patients = 3,240)								
Randomized studies (n = 6)	260	1,366	279	1,366	0.92	0.75	1.12	44%

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio.

The need for ventilation support was reported in four randomized studies. Pooled analysis showed that the need for ventilation support was rare and that there were no statistically significant differences between the intervention group (capnography with standard monitoring) versus the comparator group (standard monitoring) for the need for ventilation support (RR 0.60; 95% CI, 0.28 to 1.29) (Table 5). There was no evidence of heterogeneity between studies (Chi2 = 0.29, df = 3, P = 0.96; I2 = 0%).49 Individual study data and the forest plot can

be found in Table 60 and Figure 8, respectively (APPENDIX 11: Detailed Outcome Results — Clinical Review).

Table 5: Pooled Analysis for Change in Clinical Management (Ventilation Support) for Adults Undergoing Procedural Sedation (Randomized Studies Only, Random Effects Model)

Change in Clinical Management (*Ventilation Support*)	Standard Monitoring + Capnography		Standard Monitoring		Effect Estimate and Measure of Heterogeneity			
	Events	Total	Events	Total	RR	95% CI		I^2
Primary analysis								
Randomized studies (n = 3)	10	1,034	17	1,034	0.60	0.28	1.29	0%

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio.

Other changes in clinical management to restore proper ventilation that could not be pooled due to variations in the definition of the outcome are reported in Table 61. Chin lift or jaw thrust was a commonly performed intervention reported by van Loon 2014,[61] with a statistically significantly greater percentage of patients experiencing the maneuver in the intervention group versus the comparator group (49.5% versus 32.1%; $P < 0.001$). Likewise, a greater percentage of patients experienced changes in patient management in the intervention group versus the comparator group in three of four studies.[19,48,61] These changes included the premature termination of sedation,[61] the use of a tongue or nasal airway holder,[48] or the use of a physician intervention (which included verbal and physical stimulation, airway realignment, supplemental oxygen, use of airway adjuncts, assisted ventilation, or intubation).[19] The number of patients requiring suction in Slagelse 2013[48] was generally similar between the intervention and comparator groups (8.0% versus 8.3%; $P = 0.89$), and there were no patients in either the control or intervention groups in Slagelse 2013[48] or Qadeer 2009[54] for which the procedure had to be discontinued, or who required the use of reversal drugs. In the study by Barnett 2016,[52] a numerically higher percentage of patients with a procedure interruption (due to hemodynamic or respiratory instability) was reported in the $ETCO_2$ group compared with the no-$ETCO_2$ group.[52] In the prospective cohort studies, the changes in clinical management were recorded only for patients who were detected as having a respiratory event; no comparative trends were evident. Among the most commonly reported changes in clinical management during procedural sedation — oxygen supplementation and ventilation assistance — there was no evidence for statistically significant differences in the frequency of occurrences between patients receiving capnography and patients receiving standard monitoring. Major changes to clinical management, such as the termination of the procedure or the use of reversal drugs, were rare, and minor changes in clinical management (such as chin lift or jaw thrust) generally occurred more frequently for patients being monitored with capnography compared with patients receiving standard monitoring.

Survival to Hospital Discharge, Discharge with Full Neurological Functioning, Hypoxia and Organ Damage

Capnography Versus Standard Monitoring: Four randomized studies[20,38,51,54] and one prospective cohort study[59] reported the rate of death or permanent disability in a study-defined outcome measure: serious adverse events. In Klare 2016,[51] one patient death was reported in the standard monitoring group, which was not found to be associated with participation in the study. There were otherwise no reported deaths or cases of permanent disability in either the intervention or the control group among the five studies that reported this outcome (Table 62).

Length of Stay in Hospital
No studies assessed the effectiveness of capnography compared with other forms of monitoring for length of stay in hospital.

Correct Placement of an Endotracheal Tube
No studies assessed the effectiveness of capnography compared with other forms of monitoring for the correct placement of an ETT.

Harms
Displacement of a Ventilation/Intubation Tube
No studies assessed the effectiveness of capnography compared with other forms of detecting displacement of a ventilation/intubation tube.

Adverse Events Related to the Capnography Device
No studies assessed the effectiveness of capnography compared with other forms of monitoring for adverse events related to the capnography device.

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation
Primary Clinical-Effectiveness Outcome
Detection of Respiratory Failure: All Reported SpO_2 Measures
Capnography Versus Standard Monitoring: One randomized study comparing capnography to standard monitoring reported outcomes based on pulse oximetry for pediatric patients undergoing procedural sedation (Table 63).[68] Oxygen desaturation was defined as SpO_2 < 95%. The proportion of patients experiencing oxygen desaturation was equivalent between the intervention and comparator groups (30% and 30%, respectively).[68]

Immediate Capnography Signal Versus Delayed Capnography Signal: One randomized study comparing an immediate capnography signal (when alveolar hypoventilation was > 15 seconds) to a delayed capnography signal (when alveolar hypoventilation was > 60 seconds) reported outcomes based on pulse oximetry for pediatric patients undergoing procedural sedation (Table 63).[65] Oxygen desaturation was defined as SpO_2 of < 95% for more than five seconds. Oxygen desaturation was detected in a statistically significantly smaller proportion of patients in the intervention group (immediate signal) versus the comparator group (10.8% versus 25%; P = 0.024).[65]

Other Clinical-Effectiveness Outcomes
Detection of a Respiratory Event
Capnography Versus Standard Monitoring: Three of four studies reported an outcome for the incidence of respiratory events during the study (Table 63).[66-68] No comparative evidence was available for the proportion of patients experiencing $ETCO_2$ abnormalities in Kannikeswaran 2011.[67] There were no statistically significant differences in the proportion of patients with detected hypoventilation in the intervention group versus the comparator group in Langhan 2015 (44% versus 47%, respectively; P = 0.87).[68] Anderson 2007[66] reported fewer adverse airway and respiratory events detected by capnography compared with events detected by standard monitoring (79% versus 100%, respectively); no statistical testing was conducted.

Time to Detection of a Respiratory Event
No studies assessed the effectiveness of capnography compared with other forms of non-invasive ventilation monitoring for time to detection of a respiratory event for pediatric patients undergoing procedural sedation.

Change in Clinical Management

Capnography Versus Standard Monitoring: Three studies reported an outcome related to a change in clinical management of pediatric patients undergoing procedural sedation (Table 65).[65,66,68] In Langhan 2015,[68] there were no statistically significant differences in the proportion of patients who received an intervention to restore normal ventilation, except for head tilt or jaw thrust, for which a statistically significantly lower percentage of patients received one of these maneuvers in the intervention group versus the comparator group (3.9% versus 14.3%; $P = 0.02$).[68] In Lightdale 2006, no patients in the intervention and comparator groups received bag-mask ventilation or sedation reversal drugs, or experienced premature termination of the procedure.[65] In the prospective cohort study,[66] the changes in clinical management were recorded only for patients who were detected as having a respiratory event, and no comparative trends were evident.

No studies assessed the effectiveness of capnography compared with other forms of monitoring for other pre-specified clinical-effectiveness outcomes for pediatric patients undergoing procedural sedation, including: survival to hospital discharge, discharge with full neurological functioning, hypoxia, organ damage, length of stay in hospital, or correct placement of an ETT.

Harms

Displacement of a Ventilation or Intubation Tube

No studies assessed the effectiveness of capnography compared with other forms of detecting for displacement of a ventilation or intubation tube for pediatric patients undergoing procedural sedation.

Adverse Events Related to the Capnography Device

One study reported outcomes related to adverse events due to capnography (Table 66). Lightdale 2006[65] reported no adverse events related to the capnography device or participation in the study.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

Primary Clinical-Effectiveness Outcome

Survival of Acute Event

Capnography Versus No Capnography: One study reported the rate of survival of the CPR event (Table 67).[1] The proportion of patients reported to have survived the acute event was approximately double in the group that had documented use of $ETCO_2$ compared with the group that had no record of $ETCO_2$ use (28.3% versus 14.2%, respectively), although no formal statistical testing was reported or conducted.

Other Clinical-Effectiveness Outcomes

Return of Spontaneous Circulation

Capnography Versus No Capnography: One study reported the number of patients who were documented as having had a sustained ROSC following CPR (Table 67).[1] The proportion of patients reported to have a sustained ROSC was approximately double in the group that had a documented use of $ETCO_2$ compared with the group that had no record of $ETCO_2$ use (28.3% versus 14.2%, respectively; odds ratio [OR] 2.39; 95% CI, 1.29 to 4.46).

Effectiveness of Chest Compressions

No studies assessed the effectiveness of capnography, compared with other forms of non-invasive respiration and ventilation monitoring, for monitoring the effectiveness of chest compressions for adult patients undergoing CPR.

Detection of Respiratory Failure
No studies assessed the effectiveness of capnography, compared with other forms of non-invasive respiration and ventilation monitoring, for the detection of respiratory failure for adult patients undergoing CPR.

Detection of a Respiratory Event
No studies assessed the effectiveness of capnography, compared with other forms of non-invasive respiration and ventilation monitoring, for the detection of a respiratory event for adult patients undergoing CPR.

Change in Clinical Management
No studies assessed the effectiveness of capnography, compared with other forms of non-invasive respiration and ventilation monitoring, for changes in clinical management for adult patients undergoing CPR.

Survival to Hospital Discharge
Capnography Versus No Capnography: One study reported the number of patients who survived to hospital discharge following an out-of-hospital CPR event (Table 69).[1] There were no statistically significant differences in the number of patients having a record of survival to hospital discharge in the intervention (documented use of $ETCO_2$) and comparator group (no documented use of $ETCO_2$) (1.9% versus 2.1%, respectively; $P = 0.924$).

No studies assessed the effectiveness of capnography compared with other forms of non-invasive ventilation monitoring for all remaining pre-specified clinical-effectiveness outcomes: discharge with full neurological functioning, hypoxia, length of stay in hospital, or correct placement of an ETT for adult patients undergoing CPR.

Harms
Displacement of Ventilation/Intubation Tube
No studies assessed the effectiveness of capnography, compared with other forms of non-invasive ventilation monitoring, for detecting the displacement of ventilation/intubated tube for adult patients undergoing CPR.

Adverse Events Related to the Capnography Device
No studies assessed the effectiveness of capnography, compared with other forms of non-invasive ventilation monitoring, for adverse events related to the capnography device.

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation
No studies met the inclusion criteria of the clinical review for pediatric patients undergoing CPR.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult patients in Serious or Critical Condition
Primary Clinical-Effectiveness Outcome
Detection of Respiratory Failure
No studies assessed the effectiveness of capnography compared with other forms of monitoring for the detection of respiratory failure for adult patients in serious or critical condition.

Other Clinical-Effectiveness Outcomes
No studies assessed the effectiveness of capnography compared with other forms of monitoring for other pre-specified clinical-effectiveness outcomes for adult patients in serious or critical

condition, including detection of a respiratory event, time to detection of a respiratory event, change in clinical management, discharge with full neurological functioning, hypoxia, organ damage, and length of stay in hospital.

Survival to Hospital Discharge

Capnography Versus Standard Monitoring: The odds of death between patients monitored with capnography compared with those patients not monitored with capnography were reported in one study.[69] There was no statistically significant difference in odds of death in the intervention versus the comparator group (OR < 0.001; 95% CI, < 0.001 to > 100) (Table 70).

Correct Placement of an Endotracheal Tube

Capnography Versus Standard Monitoring: One study assessed the odds of unrecognized misplaced intubation between patients monitored with capnography versus patients not monitored with capnography.[70] There were no cases of unrecognized misplaced ETT when patients were monitored with capnography; of those patients not monitored with capnography, 23.3% experienced an unrecognized misplaced ETT insertion (OR 28.6; 95% CI, 4.0 to 122.0), and 15% of patients who did not receive capnography for out-of-hospital ETT insertion died due to unrecognized improper ETT placement (Table 71).

Harms

No studies assessed the effectiveness of capnography compared with other forms of detecting the displacement of a ventilation/intubation tube, or for adverse events related to the capnography device for adult patients in serious or critical condition.

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Primary Clinical Effectiveness Outcome

Detection of Respiratory Failure

Capnography Versus Standard Monitoring: Hawkes 2015[73] and Kong 2013[71] both reported an outcome related to the number of patients experiencing respiratory failure upon admission to the ICU (Table 72). Hawkes 2015[73] compared the percentage of patients with normocapnia between the intervention and the comparator groups; there were no statistically significant differences between the groups for the percentage of patients with PCO_2 within the target range of 5 to 8 kPa (approximately 37.5 mm Hg to 60 mm Hg) between the intervention and comparator groups (56.8% versus 47.9%, respectively; $P = 0.396$). Kong 2013[71] compared the percentage of patients with PCO_2 abnormalities (PCO_2 outside the target range of 40 mm Hg to 60 mm Hg). There were no statistically significant differences between the intervention and comparator groups (37.5% versus 33.3%, respectively; $P = 0.763$).

Other Clinical-Effectiveness Outcomes

Detection of a Respiratory Event

Capnography Versus Standard Monitoring: Kong 2013[71] and Kugelman 2015[72] reported an outcome related to the number of patients experiencing a respiratory event (Table 73). Kong 2013[71] compared the percentage of patients with $ETCO_2$ abnormalities (on admission to the ICU) between the intervention and comparator groups. There were no statistically significant differences between the groups in the proportion of patients with $ETCO_2$ outside of the target range of 40 mm Hg to 60 mm Hg between the intervention and comparator groups (33.3% versus 52.6%, respectively; $P = 0.236$). When the percentage of time spent outside an unsafe $ETCO_2$ range during ventilation was measured for neonates in the ICU in Kugelman 2015,[72] there were statistically significant differences between the intervention and comparator groups (Table 72). On average, patients in the intervention group spent 3.8% of the time in an unsafe

high $ETCO_2$ range and 3.8% of the time in an unsafe low $ETCO_2$ range compared with patients in the comparator group who spent, on average, 8.8% in an unsafe high range and 8.9% of time in an unsafe low range (P = 0.03). In this study, the unsafe $ETCO_2$ range was defined by hypercarbia ($ETCO_2$ > 60 mm Hg) and hypocarbia ($ETCO_2$ < 30 mm Hg).

Time to Detection of a Respiratory Event
No studies assessed the effectiveness of capnography, compared with other forms of monitoring, for time to detection of a respiratory event for pediatric patients in serious or critical condition.

Change in Clinical Management
Capnography Versus Standard Monitoring: Two studies[71,72] compared outcomes related to changes in patient management (as measured by the amount of time spent on ventilation, number of blood gas samples taken, and the number of ventilator setting changes) between the intervention and comparator groups (Table 74). Between the two groups in either study, there were no statistically significant differences in the median number of days that patients spent on a ventilator (median 1.0 versus 1.5, respectively; P = 0.562;[71] median 5 versus 6, respectively; P = 0.62).[72] In one study,[71] other measures of patient management included time on continuous positive airway pressure and positive pressure ventilation. Patients in the intervention group had a lower mean number of minutes of continuous positive airway pressure and a higher mean number of minutes of positive pressure ventilation (PPV) versus the comparator group; no statistical testing was conducted. In Kugelman 2015,[72] there were no statistically significant differences in the number of arterial blood gas samples taken per hour of monitoring (median 0.22 versus 0.23, respectively; P = 0.43), or the number of ventilator setting changes per hour of recording (median 0.05 versus 0.04, respectively; P = 0.94).

Survival to Hospital Discharge
Capnography Versus Standard Monitoring: One study (Kong 2013)[71] compared the percentage of infants who survived to hospital discharge between the intervention group and the comparator group (Table 75). There were no statistically significant differences in the percentage of patients who survived to discharge in the intervention versus the comparator group (87.5% versus 95.8%, respectively; P = 0.609).

No studies assessed the effectiveness of capnography compared with other forms of monitoring for other pre-specified clinical-effectiveness outcomes for pediatric patients in serious or critical condition, including discharge with full neurological functioning, hypoxia, or organ damage.

Length of Stay in Hospital
One study (Kugelman 2015)[72] compared the length of stay in hospital between patients in the intervention and comparator groups (Table 76).There were no statistically significant differences in the median number of days patients spent in hospital between the intervention group and the comparator group (median 51 days [range 8 to 166 days], versus 58 days [range 5 to 213 days], respectively; P = 0.87).

Capnography Versus Standard Monitoring
Harms
No studies assessed the effectiveness of capnography compared with other forms of monitoring for pre-specified harms outcomes for pediatric patients in serious or critical condition, including displacement of a ventilation/intubation tube and adverse events related to the capnography device.

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

Primary Clinical-Effectiveness Outcome

Detection of Respiratory Failure

For adult patients in post-operative care settings, no studies assessed the effectiveness of capnography compared with other forms of monitoring for the detection of respiratory failure.

Other Clinical-Effectiveness Outcomes

Detection of a Respiratory Event

Two studies compared the percentage of patients experiencing a respiratory event as detected by capnography versus the comparator group.

Capnography Versus Standard Monitoring: Hutchison 2008[32] compared the effectiveness of capnography with standard monitoring (as defined by pulse oximetry and respiratory rate measured every four hours) for the detection of respiratory events (Table 77). There was a higher percentage of patients in which respiratory depression was detected in the capnography group versus the comparator group (52% versus 8%, respectively); no statistical testing was conducted. The number of pauses in breathing while sleeping was lower in the capnography group versus the comparator group (24% versus 48%, respectively); no statistical testing was conducted.

Capnography Versus Rainbow Acoustic Monitoring: In the prospective cohort study,[74] the proportion of respiratory pauses detected by capnography was statistically significantly lower than the number of events detected by RAM (62% versus 81%, respectively; $P = 0.0461$) (Table 78).

Time to Detection of a Respiratory Event

No studies assessed the effectiveness of capnography, compared with other forms of monitoring for time to detection of a respiratory event, for adult patients in post-operative care settings.

Change in Clinical Management

Capnography Versus Standard Monitoring: One study reported an outcome related to changes in patient management (Table 79). No reversal drugs were used in either the intervention group or the comparator group in Hutchison 2008.[32]

Survival to Hospital Discharge

Capnography Versus Standard Monitoring: One study reported survival to hospital discharge (Table 80). All patients survived to hospital discharge in the intervention and comparator groups in Hutchison 2008.[32]

No studies assessed the effectiveness of capnography compared with other forms of monitoring for other pre-specified clinical-effectiveness outcomes for discharge with full neurological functioning, hypoxia, or organ damage for adult patients receiving care in a post-operative care setting.

Length of Stay in Hospital

Capnography Versus Standard Monitoring: One study reported an outcome related to the length of stay in hospital (Table 81). Patients in the capnography group had a statistically significantly longer mean duration in hospital (3.9 days versus 3.8 days, respectively; $P = 0.03$)

and a statistically significantly longer mean total time (2.9 hours versus 2.1 hours, respectively; $P = 0.03$) in the post–anesthesia care unit.[32]

Correct Placement of an Endotracheal Tube
No studies assessed the effectiveness of capnography, compared with other forms of monitoring for the correct placement of an ETT, for adult patients receiving care in a post–operative care setting.

Harms
Displacement of a Ventilation/Intubation Tube
No studies assessed the effectiveness of capnography, compared with other forms of detecting the displacement of a ventilation/intubation tube, for adult patients receiving care in a post-operative care setting.

Adverse Events Related to the Capnography Device
Capnography Versus Rainbow Acoustic Monitoring: One study reported adverse events related to the capnography device (Table 82). The percentage of time that the devices did not provide data was equivalent between capnography and RAM (< 2%); no statistical testing was conducted. The percentage of time that the capnography device was not functioning reliably was 6.1%; these data were not available for the RAM device.[74]

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Obstructive Sleep Apnea or Receiving High Doses Of Opioids in Post-operative Care
No studies met the inclusion criteria of the clinical review for pediatric patients in post-operative care settings.

5. Economic Review

5.1 Review of Economic Studies

A review of the literature was conducted to identify existing published studies on the economic value of capnography monitoring. Only one peer-reviewed costing study was identified, which was conducted in the United States.[79] This was a retrospective review of a quality improvement project that assessed and compared the number of blood-gas analyses before and after the implementation of standard continuous sidestream capnography for all mechanically ventilated patients in the pediatric ICU. The main objective of this study was to determine whether or not the implementation of capnography monitoring decreased the utilization of blood gases and, therefore, its associated costs. The results showed that, after the introduction of continuous $ETCO_2$ monitoring, there was a statistically significant decrease in the: total number of blood gases analyzed, average number of blood gases analyzed per patient, and average number of blood gases analyzed per ventilator day, compared with the same time period from the previous two years. Total charges for blood gas decreased from $2,207,804 in 2009 and $2,261,051 in 2010, to $1,544,360 in 2011, representing a total saving over a six-month period of $768,796. This costing study had several limitations, however, including reliance on observational data, not capturing all relevant costs, and not performing an incremental analysis. Its generalizability to the Canadian setting is further questionable given potential differences in clinical practice and associated health systems costs. Detailed methods and results of the economic literature search can be found in APPENDIX 1: Literature Search Strategy (literature search strategy) and APPENDIX 2: Detailed Methods and Results of the Review of Economic studies (detailed methods and results).

Even though abstracts were initially excluded from this review, given that only one peer-reviewed publication was identified as relevant to the research question, it was decided subsequently to consider conference abstracts. Two were identified on the use of capnography in sedation patients. Both abstracts investigated capnography monitoring during procedural sedation for gastrointestinal endoscopy in adults. Jopling et al.[80] created a gastroenterology cost-avoidance model to determine the net budgetary impact of capnography monitoring during procedural sedation for a typical hospital-based gastroenterology suite. The median annual cost avoidance with routine capnography monitoring was calculated as $304,234 compared with standard monitoring. Saunders et al.[81] was the only full economic evaluation that estimated the cost-effectiveness of adding capnography for moderate sedation during gastrointestinal endoscopy. The base-case result suggested that utilization of capnography reduced the proportion of patients experiencing one or more acute events (i.e., apnea, aspiration, bradycardia, desaturation, hypotension, and respiratory compromise) by 18.0% and resulted in a cost saving of $55 per procedure in one year. The authors concluded that capnography is likely to be cost-effective for monitoring moderate sedation in the US. However, limited information was available to fully assess the applicability of the findings to the specific research questions for this review.

Overall, there is little published evidence addressing the two economic research questions outlined in this review. Accordingly, a primary economic evaluation was developed to evaluate the cost-effectiveness of capnography monitoring compared with standard monitoring using, when possible, the clinical data that were collected in this review.

5.2 Primary Economic Evaluation

5.2.1 Methods

The objective of the economic analysis was to address the cost-effectiveness in the eight clinical populations outlined in the clinical review (Table 1). Due to the lack of clinical evidence found in the clinical review for the use of capnography in pediatric patients undergoing CPR or in post-operative care, economic evaluations were not conducted for these populations. Economic analyses were conducted for the remaining six patient populations, as outlined in Table 6.

Type of Analysis

The type of analysis conducted for each patient population is listed in Table 6. The original intent of the modelling exercise was to conduct cost-effectiveness analyses, although this was subject to the clinical findings.

Primary Analysis

A cost-effectiveness analysis was conducted to compare capnography plus standard monitoring with standard monitoring alone in adult patients undergoing procedural sedation and CPR. For pediatric patients receiving procedural sedation, the clinical review indicated no clear direction of the clinical benefit for capnography in terms of the proportion of patients experiencing oxygen desaturation and change in clinical management. A cost-minimization analysis (CMA) was therefore conducted to assess the cost difference between capnography and standard monitoring with standard monitoring alone.

Exploratory Analysis

Although the clinical review provided some evidence on the comparative treatment effect of capnography for adult patients in serious or critical condition and adult patients receiving post-operative care, no comparative literature was found for two key outcomes required in the model: detection of respiratory failure and detection of a respiratory event. An exploratory analysis was therefore conducted to assess the cost-effectiveness of capnography in these populations using data generalized from adults receiving procedural sedation. These data included the risk ratio of detecting a respiratory event in patients monitored with capnography and standard monitoring compared with standard monitoring alone.

For neonates in serious or critical condition, there was no clinical evidence on the use of continuous capnography for the clinical management of patients. The evaluation was able to focus only on the use of capnography for the confirmation of ETT placement. However, the required data inputs were not identified in the clinical review; therefore, a literature search was conducted outside the clinical search time frame and one comparative clinical study[82] was found. Published in 1995, it is unclear if the rates reported in that study remain reflective of current clinical practice. An exploratory cost-consequence analysis (CCA) was therefore conducted to compare the number of ETT misplacements detected as the measure of "consequence" of interest.

Target Populations and Settings

The target patient populations of interest were aligned with the clinical review and are outlined in Table 6. With the exception of CPR, where the base-case analysis was based on clinical data of patients receiving capnography for out-of-hospital cardiac arrest, capnography monitoring was used solely in the hospital setting for the remaining patient population. A secondary analysis was conducted in the CPR population in which the clinical parameters were based on a study of patients who were in hospital at the onset of their cardiac arrest.

Table 6: Target Populations, Interventions, Comparators, and Analysis Type

Population	Intervention	Comparator	Analysis Type
Adult patients undergoing procedural sedation	Capnography + SM	SM	CEA, PRM
Pediatric patients undergoing procedural sedation	Capnography + SM	SM	CMA, PRM
Adult patients undergoing CPR	Capnography + SM	SM	CEA, PRM
Neonatal patients in SCC	Capnography + clinical observation	Clinical observation	CCA, EXP
Adult patients in SCC	Capnography	No capnography	CEA, EXP
Adult patients in post-operative care	Capnography + SM	SM	CEA, EXP

CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CPR = cardiopulmonary resuscitation; EXP = exploratory analysis; PRM = primary analysis; SCC = serious or critical condition; SM = standard monitoring.

Interventions

As listed in Table 6, the intervention of interest in the economic analysis was most commonly capnography plus standard monitoring. For adults in serious or critical condition, the intervention was capnography alone. Standard monitoring differed by clinical area and the definition used in the economic analysis was based on the findings from the clinical review. Standard monitoring may have included pulse oximetry plus clinical observation for adult and pediatric patients undergoing procedural sedation and adult patients in post-operative care; auscultation for adult patients undergoing CPR; and clinical observation for neonatal patients in serious or critical condition. For adult patients in serious or critical condition, the comparator was no capnography (Table 6).

Perspective

This analysis was conducted from the perspective of a third-party payer (i.e., public health care payer) and considered direct medical-service costs associated with $ETCO_2$ monitoring, including costs of capnography, as well as physician and hospital costs for respiratory failure, neurological impairment, and in-hospital death due to respiratory failure.

Decision-analytic model

As each patient population has a unique clinical treatment pathway, decision-analytic models were developed, specific to each patient population, to assess the effectiveness and associated cost implications of capnography compared with standard monitoring. The clinical pathways and decision-analytic model were reviewed and validated by clinical experts who had experience using capnography devices across the different patient populations.

Figure 1 shows the decision-analytic model for adult and pediatric patients undergoing procedural sedation and for adult patients in post-operative care. The primary benefit of capnography is the ability to detect and manage respiratory events (defined as hypoventilation or respiratory depression in sedation and post-operative patients, respectively) earlier than standard monitoring, with the aim of preventing respiratory failure. The risk of organ damage and death are extremely rare in both of these patient populations, although capnography can prevent these complications. The model therefore considered the risk of developing a respiratory event, respiratory failure, and organ damage. All patients in the model were assumed not to be intubated. Those patients who did not experience a respiratory event were then considered to be alive and discharged. Monitoring patients with capnography permits the identification of patients experiencing a respiratory event and results in changes in patient

management (e.g., jaw thrusts, chin lifts) to prevent the progression to respiratory failure. In a proportion of these patients, respiratory failure is averted and these patients are assumed to remain alive and discharged; whereas, in another proportion, respiratory failure may subsequently develop. Those experiencing respiratory failure were then considered either to be alive and discharged (with or without organ damage), or to have died in hospital.

Figure 1: Model for Adult and Pediatric Patients Undergoing Procedural Sedation and for Adult Patients in Post-operative Care

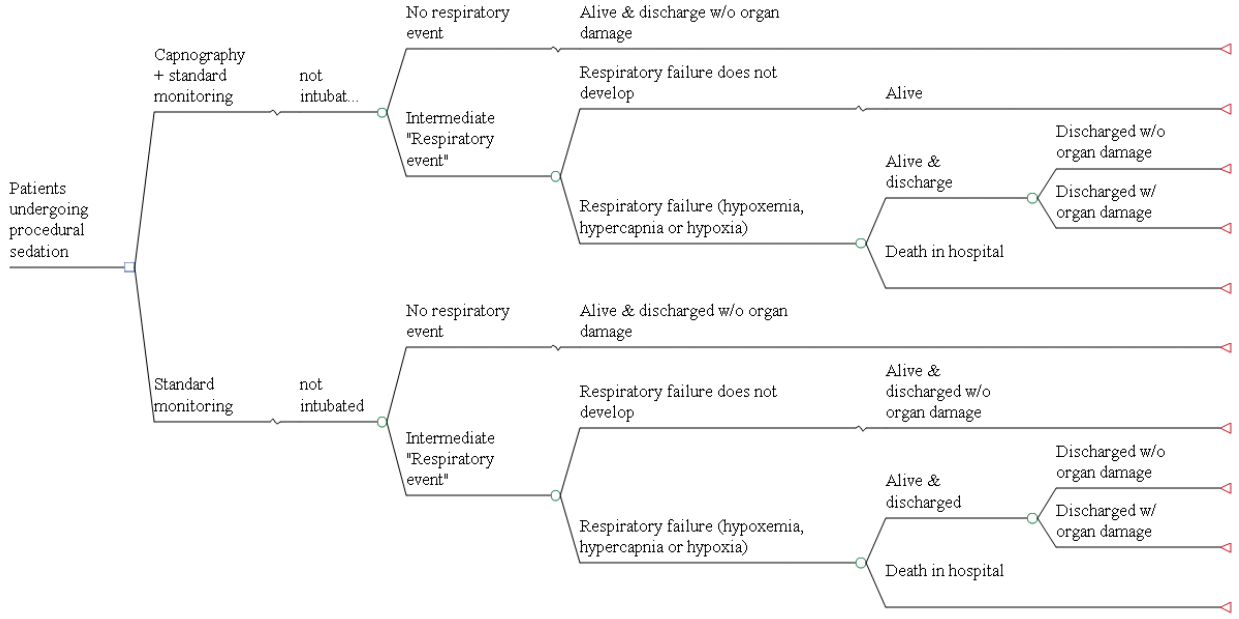


Figure 2 shows the model for adult patients undergoing CPR. This model was designed to reflect the clinical benefit of capnography with regard to the detection of an incorrect ETT placement, the likelihood of ROSC, and the risk of organ damage. To reflect clinical practice, the model considers all patients as being intubated. The ETT can be placed either correctly or incorrectly. For patients with incorrect ETT placement, the misplaced ETT can either be detected or undetected by the monitoring modality. If misplacement of the ETT is detected, the ETT will be adjusted and, in patients with correct and corrected ETT placements, they may survive or die from the acute cardiac event. In patients who survive the acute event, a proportion will survive to hospital discharge, with or without organ damage arising due to delays in return to circulation. Based on clinical experience, a misplaced ETT that is not detected is associated with a very low chance of survival. However, as no clinical literature was identified on the prognosis of patients undergoing CPR with misplaced and uncorrected ETTs, the model made an assumption that such cases would lead to death.

The model for adult patients in serious or critical condition considered the impact of monitoring on the detection of an incorrect ETT placement, the risk of developing respiratory failure, and the risk of organ damage. Representation of the model structure for this population is shown in Figure 3. All patients began the model with ETT intubation that may be either correctly or incorrectly placed. For patients with an incorrect ETT placement, the different monitoring modalities will be able to, at different rates, detect the misplacement. If misplacement is detected, the placement of the tube will be corrected. In patients with correct and corrected ETT placement, some may develop respiratory failure and, subsequently, organ damage. Capnography monitoring is intended to lead to earlier detection of hypoventilation, prompting

changes in patient management (e.g., jaw thrusts, chin lifts), and a reduction in the risk of developing respiratory failure. Patients with undetected misplacement of their ETT may either die in hospital, or be alive and discharged with or without organ damage.

Figure 2: Model for Intubated Adult Patients Undergoing CPR (Identical Decision Pathway in Both the Intervention and Comparator Strategies)

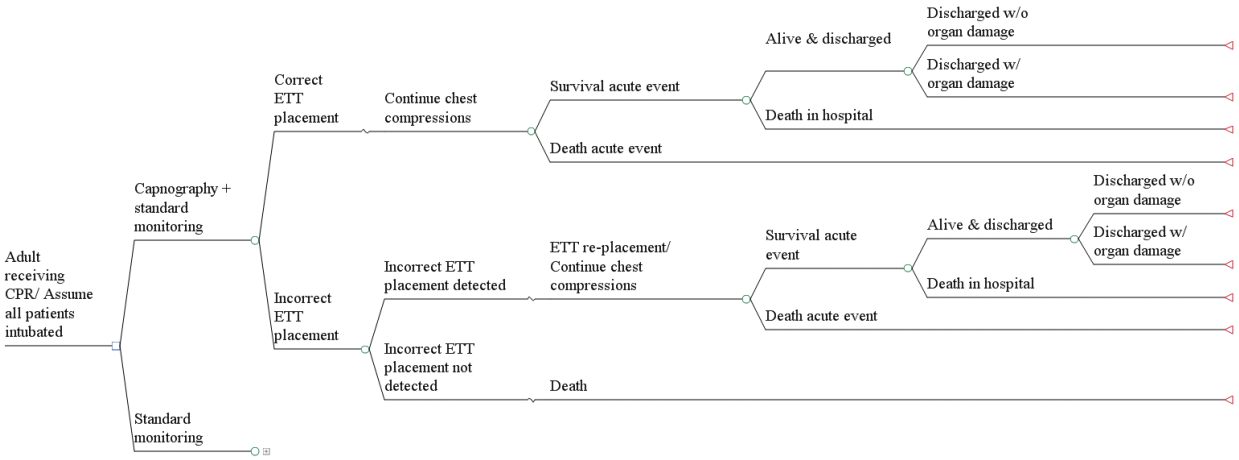
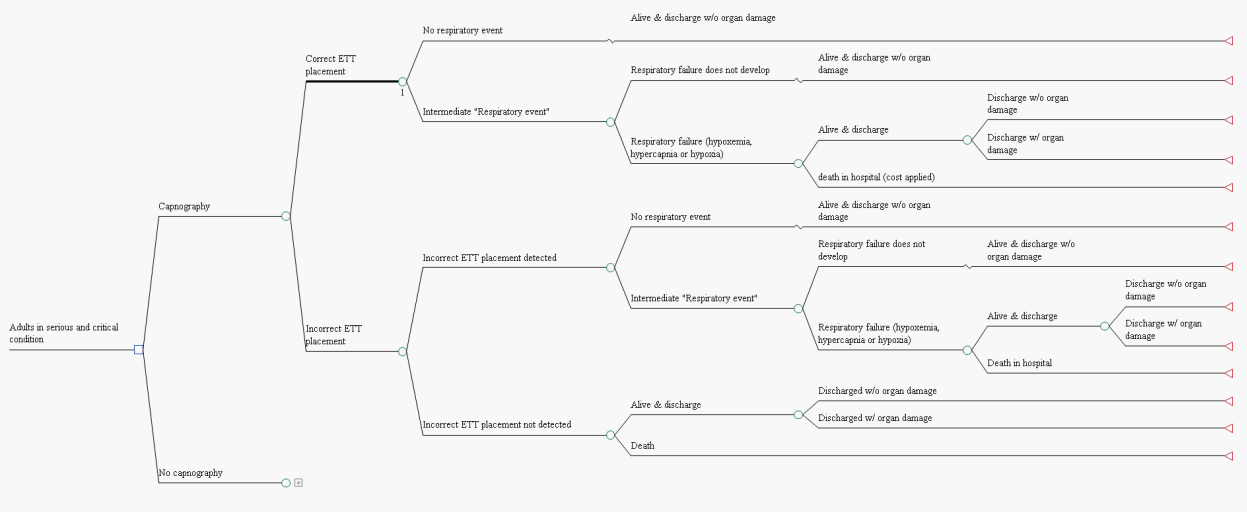


Figure 3: Model for Intubated Adult Patients in Serious or Critical Condition (Identical Decision Pathway in Both the Intervention and Comparator Strategies)



All analyses were conducted using TreeAge Pro (TreeAge Software Inc., Williamstown, MA).

Clinical Inputs

The clinical inputs required for each target population are shown in Table 83, Table 84, and Table 85 (APPENDIX 12: Clinical and Cost Inputs for the Economic Model). When possible, these data were derived from the pooled analysis of the findings in the clinical review (Table 2, Table 4, and Table 5). The published literature was searched to collect data that were unavailable from the clinical review. As some of the respiratory parameters for adult patients in serious or critical care and for adult patients in post-operative care were unavailable in the present literature, these data were generalized from the clinical findings for patients undergoing procedural sedation (APPENDIX 12: Clinical and Cost Inputs for the Economic Model, Table 84).

For the adult CPR population, two studies were identified that provided data on the probabilities for ROSC and survival to hospital discharge. The first study, identified as part of the clinical review, was an observational study conducted in Taiwan by Chen et al.[1] Given concerns with the generalizability of this study, a secondary analysis was conducted using parameters from Phelan et al.[83] Phelan et al.[83] reported considerably higher probabilities of survival (i.e., probability of survival of acute event: capnography [53.6%] versus auscultation [48.7%]; probability of survival to hospital discharge: capnography [35.19%] versus auscultation [33.82%]) compared with the probabilities reported in Chen et al.[1] (i.e., probability of survival of acute event: documented use of $ETCO_2$ [28.3%] versus no documented use of $ETCO_2$ [14.2%]; probability of survival to hospital discharge: documented use of $ETCO_2$ [1.9%] versus no documented use of $ETCO_2$ [2.1%]). Although the study by Phelan et al.[83] was conducted in the US and Canada, it was considered a secondary analysis, given that the number of ETT placements confirmed by capnography and an esophageal detector device were reported as a combined group. It is unclear what proportion of ETT placements were detected by capnography and what proportion were confirmed by the esophageal detector device. These data would have allowed an independent assessment of the comparative effectiveness of capnography for confirming ETT placement compared with auscultation.

Cost Inputs

Cost data included physician and hospital services that are associated with treatment for respiratory failure, neurological impairment, and in-hospital death due to respiratory failure (APPENDIX 12: Clinical and Cost Inputs for the Economic Model, Table 86). Costs that applied to both the standard monitoring group and the standard monitoring plus capnography group were not considered because they were equivalent to each other and would have no impact on the cost-effectiveness results. These included the costs of standard monitoring.

The cost data were primarily obtained from Ontario sources, with physician costs obtained from the Schedule of Benefits for Physician Services, while hospital costs for respiratory failure and in-hospital death were taken from the Ontario Case Costing Initiative. The cost of treatment for organ damage was obtained from an Ontario study.[84] If necessary, details on resource utilization were informed by the clinical experts involved in this review. For instance, it was noted that patients with endotracheal intubation would have had their supplemental oxygen maximized, regardless of monitoring method. As such, change in clinical management (with oxygen supplementation) was not captured in those economic models that assumed patients were already intubated at the start of the model (e.g., CPR and serious or critical condition).

The cost of $ETCO_2$ monitoring by capnography was also included. The purchase price of capnography and the cost of the associated consumable supplies were obtained from a program in British Columbia *(*Richard Milo, KGH Respiratory Services, Kelowna, BC: personal communication, November 2015). Since the cost data of ETT placement and supplemental oxygen was limited, it was derived based on an economic evaluation by Saunders et al.[85] US dollars reported in this study were converted to Canadian dollars using purchasing power parity data collected from Statistics Canada. One-way sensitivity analysis was conducted by varying these costs to test their impact. All costs were converted to 2015 Canadian dollars using the Canada Consumer Price Index.

Model Outputs

The outputs generated from the models were as follows:

- Incremental cost per averted respiratory failure for adult patients undergoing procedural sedation and in post-operative care
- Total cost per patient for pediatric patients undergoing procedural sedation
- Number of ETT misplacements detected and the associated costs for neonatal patients in serious or critical condition
- Incremental cost per life saved for adult patients undergoing CPR and for adult patients in serious or critical condition.

Sensitivity Analysis

Sensitivity analyses were conducted to evaluate the degree to which the uncertainty in cost and effectiveness parameters impacted the models' findings. The base-case findings for the full economic evaluations (i.e., CEA and CMA) represent the probabilistic results based on 5,000 Monte Carlo simulations of the parameters' distributions listed in Table 83, Table 84, Table 85, and Table 86. The probabilistic results capture the extent to which parameter uncertainty may impact the cost-effectiveness of the model. For the CCA, the base-case analysis presents the deterministic results.

For populations in which a CEA was undertaken, one-way sensitivity analyses were performed on the lower and upper range of each model input to address its impact on the incremental cost-effectiveness ratio (ICER), and the findings are presented by a tornado diagram. When

possible, the high and low parameter ranges were based on the reported 95% CI. If this could not be determined or calculated, the high and low values were based on ± 20% of the parameter's mean value. For the primary CEA, a more detailed one-way sensitivity analysis was conducted on the top five inputs that had an impact on the ICER, based on the tornado diagram.

Scenario analyses were conducted to characterize the impact of different model assumptions. In all primary full economic evaluations (i.e., CEA and CMA), a two-way sensitivity analysis was conducted. This was done by simultaneously varying the purchase price of capnography and the number of patients the device served so as to assess the impact of both model parameters on the overall ICER. An additional analysis was conducted in the model for procedural sedation in adults that simultaneously varied the baseline respiratory failure rates and the relative risk of respiratory failure.

To assess structural uncertainty in the assumption that supplemental oxygen and ventilation assistance are independent in the adult procedural sedation model, an additional one-way sensitivity analysis was conducted that varied the proportion of patients receiving both supplemental oxygen and ventilation assistance.

For the exploratory full economic analysis (i.e., adult patients in serious or critical condition or adult patients receiving post-operative care), the relative treatment effects of monitoring those patients were assumed to be consistent with the treatment effects of the adult patients who underwent procedural sedation. To assess the impact of this assumption on the cost-effectiveness results, a one-way sensitivity analysis was conducted using a wider range of uncertainty for the relative treatment effect generalized from the adult procedural sedation model.

Time Horizon and Discount

The time horizon for the economic analysis was from the start of $ETCO_2$ monitoring until hospital discharge. Given that the time horizon was less than one year, cost and health outcomes were not discounted.

Model Validation

Face validity was performed by presenting the problem formulation, model structure, and the data inputs to two Canadian clinical experts with experience in using capnography in the various clinical populations. The discussion helped ensure that the model, its parameters, and the assumptions reflected clinical practice and the available evidence. In addition, internal validity was assessed by ensuring the mathematical calculations were performed correctly and were consistent with the model's specifications. Both the model's parameters and its equations were reviewed by at least two members of the research team to ensure the data were correctly assigned. Furthermore, the implementation of the equations into the model was verified by several members of the research team. Given the paucity of clinical literature in this field, other forms of validity (cross validity, external validity, and predictive validity) could not be assessed.

Model Assumptions

The economic analyses were conducted based on the assumptions listed in Table 7.

Table 7: Assumptions Used to Populate the Economic Models

Assumption	Population
Costs that apply to both arms of the model were excluded.	All populations
The lifetime of the capnography device was assumed to be five years, and purchase cost was therefore amortized over that time period.	All populations
Patients were assumed to independently receive ventilation assistance and supplemental oxygen for the treatment of respiratory failure; the costs of both were included in the analysis.	Adults undergoing procedural sedation, in post-operative care, or in serious or critical care
Patients were assumed not to be intubated at the start of the model.	Adult and pediatric patients undergoing sedation and adults in post-operative care
All patients were assumed to be intubated at the start of the model.	Adults undergoing CPR or adults and neonates in serious or critical care
The relative treatment effects of monitoring (with respect to the prevention of a respiratory event) were assumed to be consistent with the treatment effects observed in adults undergoing procedural sedation.	Adult patients in serious or critical condition or in post-operative care
With respect to the prevention of a respiratory event, the treatment effect was assumed to be the same for both capnography and standard monitoring.	Pediatric patients undergoing procedural sedation
It was assumed that all patients survived to hospital discharge following respiratory failure, and none were discharged with organ damage.	Pediatric patients undergoing procedural sedation
The survival rate was assumed to be zero if ETT misplacement was not detected.	Adults undergoing CPR; neonates in serious or critical condition

CPR = cardiac pulmonary resuscitation; ETT = endotracheal tube.

5.2.2 Results

Base-Case Results

Research Question 9: Cost-Effectiveness of $ETCO_2$ Monitoring for Adult Patients

Primary Analysis

Table 8 presents the probabilistic cost-effectiveness results of capnography plus standard monitoring, compared with standard monitoring alone, in the adult population. The total expected cost per patient ranged from $61 to $1,019 for capnography plus standard monitoring, and $26 to $954 for standard monitoring alone. In adults who received procedural sedation or experienced out-of-hospital cardiac arrest, capnography was more costly than standard monitoring, with an incremental cost of $35 and $65, respectively. Capnography monitoring was more effective in both cases with lower respiratory failure rates (0.199 versus 0.283, respectively) in adults undergoing procedural sedation and higher survival rates (0.003 versus 0.005, respectively) in adults receiving CPR. The additional cost per averted respiratory failure was $413 for adults receiving procedural sedation, and the additional cost per life saved was $27,269 for out-of-hospital cardiac arrest adult patients receiving CPR.

Exploratory Analysis

Exploratory analysis of the adult population in serious or critical condition or in post-operative care indicated that capnography was associated with both a lower cost and improved effectiveness. Therefore, capnography was deemed to be the dominant monitoring method (Table 8).

Table 8: Probabilistic Cost-Effectiveness Results for Adults Across the Different Clinical Applications of $ETCO_2$ Monitoring

Strategy	Cost (SD)	Incremental Cost	Effectiveness (SD)	Incremental Effectiveness	ICER
Primary Analysis: Procedural Sedation — Adults					
SM	$26.13	Ref	0.283[a]	Ref	
Capnography + SM	$60.85	$34.72	0.199[a]	0.084	$413.33
Primary Analysis: CPR (Clinical Data From Chen et al. [1]) — Adults					
SM	$953.79	Ref	0.003[b]	Ref	
Capnography + SM	$1,019.23	$65.45	0.005[b]	0.002	$27,269.42
Exploratory Analysis: SCC — Adults					
SM	$10,890.64	Ref	0.810[b]	Ref	
Capnography + SM	$7,219.40	–$3,671.24	0.872[b]	0.062	Dominant
Exploratory Analysis: Post-operative — Adults					
SM	$101.90	Ref	0.038[a]	Ref	
Capnography + SM	$100.02	–$1.88	0.027[a]	0.011	Dominant

CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio; ref = reference; SCC = serious or critical condition; SD = standard deviation; SM = standard monitoring.
[a] Effectiveness defined as rate of respiratory failure for other settings. Lower rate of respiratory failure indicates better effectiveness.
[b] Effectiveness defined as survival rate.

Research Question 10: Cost-Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients

Table 9 presents the probabilistic cost-effectiveness results of capnography plus standard monitoring, compared with standard monitoring alone, in pediatric patients undergoing procedural sedation. A CMA was undertaken, given that the findings of the clinical review found no evidence to suggest a difference between the monitoring strategies for the management of patients and for the development of respiratory events. The expected costs of capnography with standard monitoring was $48 more than standard monitoring alone.

An exploratory analysis was conducted for neonatal patients in serious and critical condition, given that one study was identified outside the range of the clinical review search date. The cost-consequence analysis ound that capnography was more costly than standard monitoring with an additional cost of $50 per patient. Capnography led to fewer undetected ETT misplacements (0.0067 versus 0.022, respectively). Table 10 presents a detailed breakdown of the cost and outcomes from this analysis.

Table 9: Probabilistic Cost-Minimization Results in the Pediatric Population Undergoing Procedural Sedation

Strategy	Cost (SD)	Incremental Cost	Effectiveness (SD)	Incremental Effectiveness	ICER
Primary Analysis: Procedural Sedation — Pediatrics[a]					
SM	$66.86	Ref			
Capnography + SM	$115.13	$48.27			

ref = reference; SD = standard deviation; SM = standard monitoring.
[a] A cost-minimization analysis was conducted and, as such, there was no effectiveness presented.

Table 10: Exploratory Deterministic Cost-Consequence Analysis for Pediatric Patients in Serious or Critical Condition, Per Patient

	SM	Capnography + SM	Difference (Capnography Plus SM – SM Alone)	% Change
Cost				
Cost of additional monitoring (i.e., capnography)	0	$48.33	$48.33	NA
Cost of correcting misplacement of ETT	$38.69	$41.16	$2.47	6.4%
Total Cost	$38.69	$89.49	$50.8	131.3%
Consequences/Events				
Proportion of patients with incorrect ETT placement undetected	0.022	0.0067	0.0153	70%

ETT = endotracheal tube; NA = not applicable; SM = standard monitoring.

Sensitivity Analyses

Research Question 9: Cost-Effectiveness of $ETCO_2$ Monitoring for Adult Patients

Primary Analysis

Probabilistic Sensitivity Analysis: Figure 9 and Figure 10 (APPENDIX 13: Detailed Economic Results) show the cost-effectiveness acceptability curves for the populations of adults receiving procedural sedation and adults receiving CPR. The figures were generated from the 5,000 Monte Carlo simulations and show the probabilities of capnography with standard monitoring being cost-effective over a range of willingness-to-pay (WTP) thresholds. As WTP thresholds increased, the probability that capnography with standard monitoring would likely be considered the most cost-effective option also increased. For adults receiving procedural sedation, capnography with standard monitoring had more than 50% probability of being cost-effective when the WTP threshold for averting a case of respiratory failure was greater than $425. For adults receiving CPR, capnography with standard monitoring had the highest probability of being cost-effective at WTP thresholds greater than $75,000 per life saved. However, this model was sensitive to parameter uncertainty, given that the probability of capnography with standard monitoring being the most likely cost-effective strategy rarely exceeded 55%.

Tornado Diagram Analysis: Figure 11 and Figure 12 (APPENDIX 13: Detailed Economic Results) present the tornado diagrams that show the extent to which the ICER changes over a number of inputs listed on the left side of the diagrams. In both models, the cost-effectiveness results were most sensitive to the relative clinical effectiveness of capnography in preventing final clinical outcomes (i.e., respiratory depression for procedural sedation and survival for CPR), and the baseline risks of the clinical outcome and its associated costs. A further one-way sensitivity analysis was conducted on the top five inputs that had the greatest impact on cost-effectiveness, with the findings presented in figures 13 to 24 (APPENDIX 13: Detailed Economic Results).

Scenario Analysis: Two-way sensitivity analyses were conducted to assess to what extent the model findings changed under different scenarios when two parameter inputs were varied simultaneously. Table 88 (APPENDIX 13: Detailed Economic Results) shows the changes to the ICER when simultaneously changing the baseline rates for respiratory failure and the relative risk for respiratory failure for capnography compared with standard monitoring in adults receiving procedural sedation. As shown in Table 88, as the rate of respiratory failure increased, the ICER for capnography decreased and, as the relative risk of respiratory failure for capnography versus standard monitoring approached one (i.e., no treatment difference), the ICER for capnography increased.

Table 89 (APPENDIX 13: Detailed Economic Results) shows the cost-effectiveness of capnography by varying its purchase price and the number of patients the device serves per month. As the purchase price rose and the number of patients served decreased, the ICER associated with capnography monitoring increased in both adult populations.

Structural Sensitivity Analysis: Both models relied on several key assumptions. For the model on procedural sedation, it was assumed that patients independently received ventilation assistance and supplemental oxygen for the treatment of respiratory failure. To evaluate the scenario whereby supplemental oxygen and ventilation assistance were dependent (i.e., patients receiving ventilation assistance were also the ones receiving supplemental oxygen), a ratio parameter was introduced into the model. A sensitivity analysis was conducted varying the ratio of patients receiving both interventions and the results indicated that the cost-effectiveness was robust to this assumption (APPENDIX 13: Detailed Economic Results, Figure 23).

A further sensitivity analysis was conducted to evaluate the impact of varying the probability of undetected ETT misplacement in standard monitoring for adults receiving CPR. Given that the clinical studies had mentioned no undetected ETT misplaced in the standard monitoring group, the original economic analysis assumed that the probability of undetected ETT misplacement would be 0 in both arms of the model. The sensitivity analyses indicated that the cost-effectiveness of capnography was not sensitive to changes in the number of false negatives with standard monitoring (Figure 23). This is likely because the rate of incorrect ETT placement remained low and unless the rates of incorrect ETT placement also rose, the model findings would remain robust.

Secondary Analysis of CPR Adult Model: Table 11 presents the probabilistic cost-effectiveness results of capnography plus standard monitoring, compared with standard monitoring alone, for the adult CPR model using the clinical survival probabilities from Phelan et al.[83] Given that the survival rates reported by Phelan et al. were nearly 15-fold higher than those in the Chen et al. study, the ICER associated with capnography monitoring decreased to $4,910 per life saved. Capnography with standard monitoring was most likely cost-effective when the WTP threshold was greater than $5,250 per life saved (APPENDIX 13: Detailed Economic Results, Figure 25).

Table 11: Probabilistic Cost-Effectiveness Results in Adults Receiving CPR Based on the Clinical Data From Phelan et al.[83]

Strategy	Cost (SD)	Incremental Cost	Effectiveness (SD)	Incremental Effectiveness	ICER
Secondary Analysis: CPR					
SM	$1,356.41	Ref	0.165[†]	Ref	
Capnography + SM	$1,472.88	$116.47	0.189[†]	0.024	$4,852.92

CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio; ref = reference; SD = standard deviation; SM = standard monitoring.

Exploratory Analysis: The analysis of adults in serious and critical condition and of adults receiving post-operative care was conducted using respiratory failure parameters taken from the pooled analysis of adults receiving procedural sedation from the clinical review. The cost-effectiveness acceptability curve shows that capnography with standard monitoring would remain the most likely cost-effective monitoring strategy for patients in serious or critical condition (*P* > 99%), regardless of the WTP threshold (APPENDIX 13: Detailed Economic Results, Figure 26). For adult patients receiving post-operative care, capnography with standard monitoring would be the most likely cost-effective option when WTP was greater than $2,330 (APPENDIX 13: Detailed Economic Results, Figure 27).

A one-way sensitivity analysis was conducted on the models' inputs to test their impact on the cost-effectiveness results. For the model for adults in post-operative care, the cost-effectiveness results were found to be most sensitive to the baseline risks of respiratory failure and death, along with the associated costs of that outcome (Figure 29). The model for adults in serious and critical condition was robust as, in changing the model's parameters across a range of plausible values, capnography with standard monitoring remained the dominant strategy over capnography alone (Figure 28).

Research Question 10: Cost-Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients

In the CMA on pediatric patients receiving procedural sedation, only the cost of capnography impacted the model's finding. As such, no one-way sensitivity analysis was conducted. The cost difference between the two monitoring modalities was simply the additional cost of capnography. To characterize the potential cost difference per patient based on the cost of capnography, a scenario analysis was conducted varying the purchase price of capnography and the number of patients the device serves per month. As shown, the total cost per patient receiving capnography increased as the purchase price of capnography rose, and decreased as the number of patients served increased (Table 90, APPENDIX 13: Detailed Economic Results).

Although no sensitivity analysis was conducted on the exploratory CCA of neonates in serious and critical care, it can be observed that the cost difference between treatment strategies depends primarily on any inputs that impact the cost of additional monitoring (e.g., capnography device, number of patients served, overall lifetime of capnography monitor) and the cost of correcting a misplaced ETT. Similarly, in terms of the clinical outcomes of number of incorrect ETTs undetected, this consequence is dependent on both the overall baseline risk of an ETT misplacement and the performance of the capnography device compared with standard monitoring.

6. Health Services Impact

6.1 Methods

Citations arising from the literature search were screened by two reviewers to identify studies that contained information related to implementation considerations (for example, access, training, technical support, policies, and procedures) for $ETCO_2$ monitoring using capnography in hospital and pre-hospital settings. Information from relevant studies was organized according to study setting, within which the supports and barriers of implementing capnography were identified. This information was summarized narratively, but not systematically reviewed.

6.2 Implementation Considerations

Thirty-four [8,24,86-117] citations containing information regarding barriers, supports, and other implementation issues related to the use of capnography in hospital and pre-hospital settings were identified. The identified citations reported on implementation issues in the following clinical settings: pre-hospital,[86-91] the emergency department and acute care,[8,24,92-109] the operating room,[96,110-114] and the post–anesthesia care unit.[115-117]

6.2.1 Pre-hospital Setting

Supports

Educating pre-hospital staff on the use of capnography has been suggested as a support to implementation.[87] A supportive mnemonic that mimics the "ABCs" (airway breathing, circulation) of emergency medicine has been developed for the use of $ETCO_2$ for resuscitation: P (position of the tube); Q (quality of chest compressions); R (ROSC/detection); S (strategy for further treatment); T (termination of resuscitation for maximum benefit of capnography).[89]

Barriers

The availability of capnography equipment in a transport vehicle can further increase the likelihood of its use.[90] As the set-up of the equipment can be seen as a barrier to use, a pre-assembled mask or assembled mask capnography may be feasible to use during transport and pre-hospital use.[91]

6.2.2 Emergency Department and Acute Care Settings

Supports

Based on results from surveys, interviews, guidelines, and trials, there are factors that are believed to contribute to successful implementation of capnography into regular use in the emergency department and acute care setting. With respect to staffing and human resources, staff champions[96] — having a good understanding of the principles and use of capnography,[96] educational initiatives and training,[95] familiarity with capnography literature,[97] and having a culture of change to aid in the implementation or use of new equipment[98] — have been identified as potential supports to implementing capnography. With respect to the physical work environment, the ability to quickly access capnography equipment,[96,99] and having capnography available at all bedsides in the pediatric ICU,[95] could contribute to the successful implementation of capnography. With respect to policies and procedures, supports to implementation include identifying capnography as the standard of care,[96] having a policy for its use (e.g., for all intubated patients),[24,96,101] having a legal mandate to use capnography after endotracheal intubation (as is the case in Germany),[100] having capnography listed in minimum equipment guidelines (as it is in some US states),[95] and having guidelines that support capnography for intubated patients.[102] Additional supports that have been identified include the short time that elapses between attaching a capnography device and obtaining a good reading,[96] the simplicity of using capnography equipment,[101] the user's perception of capnography being inexpensive,[97] and that it can help provide continuity of care if capnography is already used in the pre-hospital

setting.[101] In a study of emergency departments in Thailand, the implementation of an evidence-based care bundle that included airway management approaches, one of which is capnography, was found to increase the use of capnography where appropriate.[103] Some capnography interfaces are more intuitive than others or require less training.[106] For example, in one study, health care workers were slower in activating one device compared with another, even after specific training.[106] Ensuring patient safety may require both specific training and an intuitive and ergonomic interface.

Potential additional uses for capnography in the emergency department include evaluating patients with diabetic ketoacidosis,[107] seizures,[107] pulmonary embolism,[107] and malignant hyperthermia,[107] and for triage.[107,108] In the ICU, capnography may also be used for apnea testing in patients who are suspected to be clinically brain-dead.[109] It can aid in detecting spontaneous respiratory movements, and the printouts from the capnography machine would be useful for medico-legal purposes.[109] Using capnography instead of other methods (or prior to deciding if other methods are needed) can reduce the need to transport a patient who is unstable to a radiology unit, and reduce the need for contrast injections in patients for whom it is not necessary.[109]

Barriers

Lack of equipment,[97-99] lack of experience with the equipment,[97] perceived lack of need for capnography,[97] perceived lack of evidence or lack of convincing evidence for its use,[96,97] perceived difficulty[97] or lack of knowledge regarding the use and interpretation of data outputs,[96,118] expense,[97,118] the need to buy new equipment if the monitors in use do not have a capnography function,[101] and perceived inaccurate measurements have all been identified as barriers to regular capnography use.[97,118] Past negative experiences,[96] lack of experience[98] or lack of familiarity with capnography equipment,[101,118] as well as infrequent use[96] of capnography can also contribute to limited uptake. Additionally, not having mandated use can decrease the likelihood that capnography will be used in all patients for whom it is indicated.[96] Although not identified as a harm in the studies included in the clinical review, tracheostomy tube displacement during patient movement[104] is a potential capnography-related adverse event in the ICU or in immobilized patients. The capnography line may interfere with the tracheostomy if those moving the patient are unfamiliar with the locations of the lines.[104] Awareness of clinical situations where there is a potential for adverse events or where inaccurate measurements are more common, may facilitate a cautious interpretation of capnography readings in some settings.

6.2.3 Operating Room

Supports

Having capnography as the standard of care[96] has been identified as a support by health care professionals who work with patients under conscious sedation.

Barriers

Lack of unequivocal recommendations[112] and lack of mandated use[96] for conscious sedation have been identified as barriers. An additional barrier to its use in children may be a perception that the protocols are already so rigorous that early detection of respiratory events is not an issue for children under conscious sedation.[96] When sidestream devices are used during head and neck surgeries, kinking of the sampling line can occur, leading to inaccurate readings. An angled insertion of the sampling line may help mitigate that problem[113] and therefore increase both staff confidence in capnography and the likelihood of accurate readings. Additionally, advanced auditory display alarms may be more helpful than visual displays alone in alerting anesthesiology staff that there is a potential problem.[114]

6.2.4 Post-operative Care Unit

Supports

Supports identified for the successful implementation of capnography in the post-operative care unit include having established processes for training staff with respect to new devices and procedures, comprehensive protocols for the use of monitors, highly motivated staff, a pre-existing order-entry system that could include capnography, and having staff with a foundational knowledge of $ETCO_2$ monitors.[115]

Barriers

Barriers to successful implementation included a lack of clarity regarding who could prescribe the use of monitors and having an insufficient number of monitors, both of which contributed to irregular use.[115] In an American 489-bed level 1 trauma centre, 63 $ETCO_2$ monitors was seen as a "support" to uptake and implementation; a further 30 were purchased to maintain a steady supply to the post-anesthesia care unit (PACU).[115] In a survey of PACU nurses from 90 American institutions, those who had access to capnography equipment found it to be useful for detecting opioid-related sedation events; however, 75% of those surveyed could not access capnography in the PACU.[117]

7. Discussion

7.1 Summary of Results

7.1.1 $ETCO_2$ Monitoring for Adult and Pediatric Patients Undergoing Procedural Sedation

The results of our primary clinical analysis suggested that adult patients undergoing procedural sedation experienced fewer episodes of hypoxemia with the use of capnography. The clinical effectiveness of capnography for preventing severe hypoxemia in this population was less clear. For pediatric patients undergoing procedural sedation, evidence was limited and the results of our primary clinical analysis were mixed. One study found no differences in the occurrence of oxygen desaturation,[68] while one study favoured the use of capnography.[65] Study quality concerns and differences between the design of each study in the pediatric population indicate the need for cautious interpretation of these results.

For other clinical-effectiveness outcomes included in our review, capnography was found to offer increased detection of respiratory events in adults undergoing procedural sedation. It is important to note that, where a respiratory event was defined by capnography criteria only (for example, in Beitz 2012[38]), the appearance of a greater detection of respiratory events by capnography is not a fault of standard monitoring, but simply a lack of capability to detect these events as they are defined. This caveat is necessary for the appropriate interpretation of the comparison; however, it does not negate the observed benefit of capnography as an additional monitoring tool for providing information about a patient's ventilation status. Despite greater detection of respiratory events in the adult population, there was no evidence of statistically significant differences in the frequency of use (either increased or decreased), of assisted ventilation, or increases in oxygen supplementation between patients receiving capnography and patients receiving standard monitoring. Changes in clinical management, such as chin lift and jaw thrust, generally occurred more frequently for patients being monitored with capnography compared with patients receiving standard monitoring. These results support the step-wise nature of the use of clinical interventions for restoring ventilation. Minor interventions such as patient repositioning or verbal or physical stimulation are implemented first, followed by more advanced interventions such as supplemental oxygen and ventilation if a patient's condition does not improve.[119] These results, however, do not reveal the appropriateness of the

changes in clinical management that occurred, and may have overlooked the occurrence of unnecessary clinical interventions in the case of detected transient respiratory events.

In the final literature search alert update, one study was identified as meeting the selection criteria of our review for adult patients undergoing procedural sedation, but was not included in the main analysis.[120] This study was similar to the design of the study by Qadeer 2009.[54] The results of this study indicated no statistically significant differences in the number of episodes of hypoxemia or respiratory events detected for patients undergoing colonoscopy or esophagogastroduodenoscopy (EGD). The study results, however, were suggestive of differences in the number of episodes of severe hypoxemia detected, particularly for the group of patients undergoing colonoscopy.[120] While we were unable to conduct subgroup analyses in our review, this study suggested there may be evidence emerging that not all patients undergoing electoral procedures may benefit equally from capnography monitoring.

In this review's primary economic analysis for adult patients undergoing procedural sedation, the base-case incremental cost per averted respiratory failure for capnography with standard monitoring, compared with standard monitoring alone, was $377 per respiratory failure avoided. The model was found to be robust across a range of sensitivity analyses.

In the pediatric population, the clinical effectiveness of capnography was not statistically significantly different than standard monitoring in terms of its ability to detect episodes of hypoventilation and adverse airway and respiratory events, or to influence clinical management.[65,66,68] Pediatric patients may have more rapid deterioration if hypoxemia occurs, so detecting a problem with ventilation earlier is important in this population.[121,122] This review's results do not demonstrate a benefit of capnography for greater detection of respiratory events, but one study of low quality suggests that patients monitored with capnography have a reduced occurrence of oxygen desaturation.[65]

Given that there was no clear direction on the clinical benefit for capnography in terms of the proportion of patients experiencing oxygen desaturation and change in clinical management, a cost minimization analysis was conducted. Capnography with standard monitoring was assumed not to lead to the avoidance of more respiratory failures than would be avoided by standard monitoring alone; thus, the addition of capnography to standard monitoring was associated with an additional cost of $48 per pediatric patient undergoing procedural sedation.

The timeliness of interventions provided,[68] and the number of respiratory events detected[66,67] found in some studies, however, suggests that although there were not statistically significant differences in the number of respiratory failures avoided, the timeliness of the detection of respiratory events offer benefits that were not well captured in the included clinical studies and the economic evaluation.

7.1.2 $ETCO_2$ Monitoring for Adult and Pediatric Patients Undergoing CPR

There was limited evidence available to assess the effectiveness of capnography for monitoring adult patients undergoing CPR. For patients experiencing out-of-hospital cardiac arrests, there was evidence for a greater likelihood of ROSC and survival of the acute event for patients monitored with capnography;[1] however, no statistically significant differences in the proportion of patients who subsequently survived to hospital discharge were found.[1] These results should be interpreted with caution, given the low rate of exposure to capnography monitoring in the study cohort (1.6% of patients [83/5,041]).

The results of the primary economic analysis for adult patients undergoing CPR were based on the clinical results of a retrospective cohort of out-of-hospital cardiac arrest patients. The model indicated that capnography improved survival rates but at a higher cost. The ICER for the base-case analysis was $27,269 per life saved. The economic findings were found to be highly sensitive to the mortality rates used in the model. A secondary analysis was conducted using the higher survival rates that were reported by Phelan et al.[83] on a cohort of in-hospital cardiac arrest patients. Using the clinical parameters from Phelan et al.,[83] the ICER declined to $4,910 per life saved. Possible reasons for the differences in survival rates between these two studies include: countries (Taiwan[1] versus North America[83]), setting in which the cardiac arrest occurred (out-of-hospital[1] versus in-hospital[83]), and differences in study design. The base-case analysis results should be interpreted as representing the likely cost-effectiveness of capnography in patients experiencing cardiac arrest out-of-hospital. The exploratory economic analysis based on the results by Phelan et al.,[83] however, requires cautious interpretation given that the treatment group was not simply capnography, but also included esophageal detector device or $ETCO_2$ detectors to document the ETT position. As it was not possible to determine the independent clinical effect of capnography in Phelan et al.,[83] the secondary analysis using data based on Phelan et al. is likely an overestimate of the clinical and economic benefit of capnography.

As discussed earlier, the findings of the CPR economic model are highly dependent on the probability of survival. The economic model relied on the assumption that an undetected misplaced ETT would be fatal given that no clinical literature was identified on the prognosis of such patients. Although it is difficult to assess the validity of this assumption, it is important to note that the likelihood of not detecting an ETT misplacement is extremely rare. Indeed, the clinical review found no cases in which a misplaced ETT was not detected. As such, despite requiring a simplifying assumption that a misplaced ETT would be fatal if undetected, the model was likely not impacted by this assumption, given that no such cases of undetected misplaced ETT occurred.

No clinical trials were identified on the use of capnography in pediatric patients undergoing CPR and, as such, the clinical effectiveness and cost-effectiveness of capnography in this patient population remains unknown.

7.1.3 $ETCO_2$ Monitoring for Adult and Pediatric Patients In Serious Or Critical Condition

There was limited evidence to assess the effectiveness of capnography for adult patients in serious or critical condition.[69,70] Evidence suggested that patients monitored with capnography were less likely to experience an unrecognized misplaced ETT compared with patients who were not monitored with capnography.[70] Death as a result of misplaced ETT was also therefore prevented. It should be noted, however, that very few patients in the cohort were exposed to $ETCO_2$ monitoring (5.9%), one study author was a consultant for the capnography manufacturer, and the authors made no conclusions specific to capnography monitoring.[70] The interpretation of the results for this population is limited due to a lack of reporting of patient characteristics and details of the intervention and comparator in both studies.

Given the limited clinical evidence for adult patients in serious or critical condition, the economic evaluation was an exploratory analysis that relied on the assumption that the treatment effects of capnography compared with standard monitoring for the incidence of respiratory failure would be similar to what was observed in adult patients receiving procedural sedation. This exploratory analysis showed that capnography improved health outcomes at a lower cost, and therefore dominated standard monitoring. Sensitivity analysis conducted on the model indicated that capnography remained the dominant strategy — even if the relative treatment effect between

capnography versus standard monitoring was less favourable than what was reported in the procedural sedation population. It has been speculated that, in critically ill patients, there may be a greater benefit to earlier detection of respiratory compromise, given that these patients have less cardiorespiratory reserve compared with those undergoing procedural sedation. This would mean that the magnitude of the relative treatment effect would be larger than procedural sedation. If this were the case, the existing exploratory analysis can be seen as providing a more conservative estimate of the potential economic value of capnography when compared with standard monitoring. Similarly, the rate of misplaced ETT undetected by standard monitoring (i.e., 23%) used in the economic model may be higher than what would be expected within a conventional hospital setting as these values were taken from a study conducted in an out-of-hospital setting.[70] Despite these concerns, sensitivity analysis found that the model's findings remained robust even when varying this parameter value. Overall, the model remained robust across a range of sensitivity analyses and this was likely driven by the higher costs of treating respiratory failure in this patient population.

The studies that met the inclusion criteria for pediatric patients in serious or critical condition included preterm newborns, or newborns who were receiving ventilation and were at high risk of needing resuscitation. One study found a statistically significant difference in the percentage of time that patients spent in an unsafe high or an unsafe low $ETCO_2$ range.[72] This finding deserves cautious interpretation due to the methodological concerns of the study. There were otherwise no statistically significant differences in the detection of respiratory events, number of respiratory failures, changes in clinical management, rates of survival, or length of stays in hospital in the included studies.[71-73] Adoption of $ETCO_2$ monitoring for pediatric patients in the ICU was initially challenged because the devices were too large.[123] The evolution of capnography devices has enabled more widespread use in the pediatric population,[123-126] including neonates; however, there is still limited evidence, with most evidence based on observational trials.[123]

Given that the clinical review found limited evidence for the use of capnography in this patient population, an additional article was identified from a literature search beyond the original 10-year time frame. This was the main paper to support an exploratory CCA to assess the costs of capnography and the rate of detecting misplaced ETTs with capnography in this patient population. Capnography was associated with fewer cases of undetected ETT misplacements (< 1% versus 2.2%) and costs were, on average, $89 per patient compared with $39 in the standard monitoring group. However, it is important to note that the clinical study supporting this exploratory analysis was published in 1995 and it is not clear whether the false negatives rates (i.e., undetected ETT misplacements) have remained constant and are appropriate to current clinical practice, despite technological progress in capnography devices. The single costing study identified in the review of the economic literature found differences in the utilization of blood gases before and after the implementation of standard continuous sidestream capnography for all mechanically ventilated patients in the pediatric ICU. This translated to a decline in the total annual charge for blood gas, ranging from $2,207,804 to $2,261,051 before the introduction of capnography, to $1,544,360 with the introduction of capnography. It should be noted that this costing study did not measure changes in patient outcomes following the introduction of capnography, and it did not include the upfront purchase and maintenance costs of the capnography device.

7.1.4 $ETCO_2$ Monitoring for Adult and Pediatric Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids In Post-operative Care

There was no evidence to assess the effectiveness of capnography compared with other forms of monitoring for the detection of respiratory failure for adult patients in post-operative care

settings. For other clinical-effectiveness outcomes, compared with standard monitoring, one study found that patients in the PACU following orthopedic surgery who were monitored with capnography were more likely to have a respiratory event detected, and to have fewer pauses in breathing while sleeping.[32] These results, however, are difficult to interpret given that the study stated the respiratory events were detected by respiratory rate changes or apnea detection, and not by pulse oximetry or capnography, and that one study author received a speaking honorarium from the capnography manufacturer. Compared with RAM, patients monitored with capnography were statistically significantly less likely to have a respiratory pause detected.[74] It should be noted that in this study, research personnel and study authors received funding from the rainbow acoustic monitor manufacturer, and one author was employed by the same manufacturer. Similar to the findings for adult patients in serious or critical condition, the limited clinical evidence led to an exploratory economic evaluation. This evaluation was based on the assumption that, compared with standard monitoring, the treatment effects of capnography for the incidence of respiratory failure would be similar to what was observed in adult patients receiving procedural sedation. The results showed that capnography improved health outcomes at a lower cost for adults in post-operative care, and therefore dominated standard monitoring.

Opioids are commonly used in the post-operative period for the management of pain,[127] during which time opioid-induced respiratory depression is possible. For the two studies included in our review, 97%[74] and 100%[32] of patients were prescribed post-operative pain medication. The extent of patient monitoring is dependent on several factors, such as the details of the procedure, patient comorbidities, presence and severity of sleep apnea, and the capabilities of the hospital facility.[128] These and other factors can increase a patient's risk for respiratory depression when opioids are administered.[127]

No clinical trials were identified on the use of capnography in pediatric patients in post-operative care and, as such, the clinical effectiveness and cost-effectiveness of capnography in this patient population remains unknown.

7.1.5 Harms

For studies that reported harms data, there were no significant differences to note between capnography and other forms of ventilation monitoring. The use of capnography has been associated with the occurrence of false-positive results; however, it is unclear how such events influence patient management and outcomes. False-positive events may result from the ingestion of carbonated beverages prior to monitoring,[129] from the displacement of the supplemental oxygen line,[37] or from leaks in the sampling devices or ventilator circuit.[6] For example, in infants and neonates, uncuffed ETTs are often used to protect airways and there is the risk of leakage when this is done.[105] Patients may also experience $ETCO_2$ changes suggestive of respiratory depression but with no subsequent hypoxia, a finding apparent in several studies included in our review.[51,55,57,59] In the latter case, these changes may be due to false-positives, an intervention provided by the clinical team, or due to spontaneous resolution of the event. As this is a medical device that requires calibration, there may also be concerns about incorrect calibrations of the monitoring device, as was the case in the medical device recall of the Alaris $ETCO_2$ modules.[130]

7.2 Generalizability of Findings

Following the search criteria used for our clinical review, there were two systematic reviews,[21,131] one of which included a meta-analysis,[21] identified in the published literature to enable a comparison with our results. This meta-analysis assessed the effectiveness of capnography for

detecting respiratory events in adult patients undergoing procedural sedation.[21] The results of this study are similar to those found in our review, indicating that the use of capnography in addition to standard monitoring resulted in greater detection of respiratory events. This study did not assess the impact of capnography monitoring on the occurrence of hypoxemia, changes in clinical management, or other outcomes of interest in our review. The other systematic review identified from the literature assessed the use of all forms of CO_2 monitoring for preterm newborns in the delivery room.[131] The review identified capnography as offering more timely and accurate confirmation of ETT placement compared with clinical assessment.[132] Our review, however, was not meant to systematically assess the accuracy of capnography for detecting ETT placement. Two other systematic reviews,[133,134] one of which included a meta-analysis,[133] were identified that assessed the relationship between $ETCO_2$ values and ROSC, with the goal of identifying an optimal $ETCO_2$ value during CPR,[133] or as a prognostic indicator of outcome following CPR;[134] however, these outcomes were not of interest in this review. While we recognize that a similar systematic review[39] was being undertaken at the same time as our HTA, the anticipated completion date and the project scope indicated in this protocol necessitated this CADTH review.

Across patient populations, several clinical practice guidelines suggest that capnography should be used or should be considered for use in certain clinical situations. For patients undergoing procedural sedation, the guidelines state that capnography should be considered for certain patients (those with a Ramsay sedation score of 4 to 6,[7] patients undergoing deep sedation,[135,136] those for whom clinical assessment is not possible,[136] high-risk patients[135]) or for long procedures.[135] In post-anesthesia care units, on the other hand, clinical practice guidelines suggest that pulse oximetry is the monitoring method of choice for patients during the initial phase of recovery,[7] for patients who are at increased risk of respiratory compromise,[137] and as a minimum addition to clinical monitoring in immediate post-anesthesia settings.[116] Other guidelines suggest capnography be standard for health care procedures,[138] as an adjunct to pulse oximetry and clinical assessment for procedures in the emergency department,[11] be used according to the clinical status of the patient,[139] and as a minimum monitoring method for patients undergoing bariatric surgery.[128] The availability of guidelines and policies for the use of capnography has been found to be supportive of successful implementation of the device.[24,96,101,115]

Capnography is also commonly the monitoring method of choice in clinical practice guidelines that apply to the management of patients who are intubated or are undergoing intubation. For patients undergoing CPR, capnography has been described as having application as a device to: guide the placement of an ETT, monitor ventilation status, guide the effectiveness of chest compressions, and predict survival during resuscitation.[26,27,140] Several reviews and clinical practice guideline documents[8,141,142] have highlighted these applications. Clinical practice recommendations for intensive care services[143] and respiratory care[6] also recommend the use of capnography for all airway placements. The Canadian Paediatric Society's position statement on the inter-facility transport of critically ill newborns suggests that capnography devices (either end-tidal CO_2 or transcutaneous) be used as part of the suite of neonatal transport equipment,[144] and the UK Resuscitation Council guidelines for newborn life support suggest that capnography, in addition to clinical assessment, is the most reliable method for confirming ETT placement in neonates with spontaneous circulation.[145]

The majority of the clinical evidence was from the US, generally based at urban, tertiary care, or university-affiliated centres. A minority of studies were based in Germany, Denmark, Spain, Ireland, The Netherlands, Japan, Taiwan, and Israel. The generalizability of the results to less specialized centres or rural settings, particularly for patients undergoing CPR or in serious or

critical condition, is unknown. This may have further implications for the economic model if it is suspected that the baseline rates of adverse airway or respiratory events would differ between urban and rural settings. For instance, the primarily analysis of the economic model on CPR patients was based on survival rates from one study conducted in Taiwan, and it is not clear whether the clinical parameters used in the economic model are reflective of the Canadian setting.

The majority of the cost inputs were obtained from Ontario sources and, when necessary, supplemented by costs from the US. Sensitivity analyses indicated that the cost inputs used in the cost-effectiveness analysis did not have a particularly strong influence on the results and, thus, the variance in costs that may exist across geographical regions may not be a particular concern in interpreting the cost-effectiveness of capnography.

The economic analyses overall highlighted a general trend that may be applicable to all patient populations included in the present review. Sensitivity analyses consistently showed that the economic value of capnography monitoring was most sensitive to the baseline risk of respiratory failure (for patients undergoing procedural sedation, in serious or critical condition, or in post-operative care) and the treatment effect size. In fact, an interaction may be present between these two parameters. Capnography would increasingly become an attractive treatment modality as the baseline risks of an adverse airway event increased and the magnitude in the treatment effect size was more in favour of capnography. Drawing conclusions about whether combined monitoring would be considered cost-effective across all Canadian jurisdictions may be difficult. Firstly, there are no common cost-effectiveness thresholds for the incremental cost per respiratory failure avoided, or cost per survival gained, that can be referenced. Furthermore, the analysis that demonstrated capnography being a dominant intervention in adults in serious or critical condition was based on an assumption of transferability of the clinical effectiveness results of capnography from the clinical outcomes observed in adult patients receiving procedural sedation. This may, in fact, not hold true, given differences in patient demographics and disease severity between these patient populations.

The availability of devices, education, and training for users; ease of use; and organizational culture are factors that may support the successful implementation of capnography monitors, and that may vary across regions. Although it is likely that similar monitoring practices would occur across geographical regions, the lack evidence from the Canadian setting is an important limitation to note when interpreting the clinical and economic findings of our review.

7.3 Study Limitations

There were several challenges and limitations encountered during this review. The primary outcome was defined in our review protocol as hypoxemia, which was defined by a pulse oximetry measure (SpO_2) for which study-specific definitions were extracted and included in the analysis. Although this approach allowed for a greater breadth of included studies, several studies reported multiple measures of hypoxemia, and the thresholds for hypoxemia varied between studies. The criteria for hypoxemia and severe hypoxemia adopted by our review were selected in consultation with clinical experts; however, we recognize that these thresholds will vary between centres and across patient populations. It is also important to note that the interpretation of the findings for the outcomes specified in this review is challenging. In several cases, a statistical interpretation of the results was possible; however, for outcomes such as the detection of respiratory failure or respiratory events, it is uncertain what magnitude of change would be sufficient to suggest a meaningful benefit in clinical practice.

There was a limited amount of data available for several patient populations and outcomes, making it difficult to provide an indication of the direction for the favourability of evidence for these outcomes in each population of interest. The lack of clinical evidence in some populations also led to an economic evaluation with a focus narrower than anticipated, or resulted in generalizing data from one clinical area to perform an exploratory analysis in another clinical area. For instance, the exploratory economic model for neonates in serious and critical condition could only address the use of capnography for ensuring correct placement of the ETT, and not for continuous monitoring of patients in intensive care. Furthermore, the parameters used in this model came from a study published in 1995,[82] and it is questionable whether the performance of capnography has remained constant over time — despite technological innovations in these medical devices. The interpretation of the results of the economic evaluation presented in this review was also challenged by the lack of published literature to serve as a comparison. Likewise, this issue is also a concern in the adult CPR and serious and critical condition analyses. As mentioned previously, the CPR model was based on a single study in Taiwan with an exploratory analysis conducted using the clinical parameters from another study given systematic differences between these two studies. Many parameters in these models were informed by single studies and, in some cases, the potential risk of bias in these studies might be high, which could then translate into the economic model. For instance, the relationship between capnography and the detection of misplaced ETT in adult trauma patients was based on a small prospective study with potential conflicts of interest that reported results favourable to capnography.[70] The magnitude of the bias that may have been introduced into the economic model is unclear. The economic evaluation was further unable to consider all potentially relevant comparators, such as colorimetric capnometry, given that comparative clinical evidence was limited.

The cost and resource utilization parameters for this model were, in some cases, limited. For instance, in the CPR model, the potential costs of patients who survive CPR and who require subsequent hospitalization were not incorporated into the model, as no literature was found on the likely monetary value in a relevant health care setting. Not including these costs may have in fact introduced bias in favour of capnography, given that the survival rates are higher for patients receiving capnography versus standard monitoring.

Due to the heterogeneity between studies in terms of study design, intervention, comparator, patient characteristics, and procedure type (for procedural sedation and post-operative recovery), we were unable to assess the differential benefit of capnography for specific patient characteristics or clinical situations. Most devices used in the included studies were sidestream, portable, multi-parameter models that were suitable for the adult, pediatric, and neonatal populations; however, there were an insufficient number of studies to assess the effectiveness of one capnography device compared with another.

While the inclusion of observational studies offered the ability to assess a greater breadth of outcomes, such as harms and adverse events, the inclusion of these studies also created challenges for the interpretation and synthesis of results. An additional challenge with the inclusion of observational studies was to understand that although a greater number of respiratory events may have been detected, we were unable to determine if the detection of respiratory events would have resulted in appropriate changes to patient management and, in turn, resulted in changes in clinical outcomes. Finally, we attempted to report as much detail as possible regarding the definition of standard monitoring for the included studies; however, the specifics of standard monitoring were variable between studies and these details were often not reported or were unclear.

7.4 Directions for Future Research

Future research would be useful on the impact of capnography on the entire continuum of care for each of the four clinical populations included in our review. This research may help explain the clinical decision-making pathway for each population and help recognize the links between detection of respiratory events, change in clinical management, incidence of respiratory failures, and clinically important end points such as morbidity and mortality. Comparative interventional research studies are needed for pediatric patients undergoing CPR and in post-operative recovery, and for adult patients undergoing CPR, in serious or critical condition, and in post-operative recovery. A clearer picture of the clinical decision-making pathway for each population, and comparative evidence in each, could inform a more complete decision-analytic framework and generate more accurate inputs for the economic model. The establishment of levels of severity for hypoxemia (for example, mild, moderate, severe, and profound), may help to encourage consistent reporting across studies and allow for a more objective assessment of study results. The systematic collection of harms data may help identify patient populations that are particularly susceptible to false alarms or technical problems with the monitoring device.

8. Conclusions

The greatest volume of clinical evidence was available for the use of capnography in adult patients undergoing procedural sedation. In this population, respiratory events were detected more frequently with capnography, and fewer patients experienced episodes of hypoxemia compared with standard monitoring. These results, when transferred into the economic evaluation, suggested that capnography offered a reduction in the number of episodes of respiratory failure, but at an additional cost. The interpretation of whether capnography is considered cost-effective is dependent on the opportunity cost associated with its adoption. If capnography is adopted for use for adult patients undergoing procedural sedation, resources must be extracted from within the health care system or new funding must be found.

For adult patients undergoing CPR, the clinical review found that capnography was associated with an increased likelihood of ROSC during out-of-hospital cardiac arrests. These results, when transferred into the economic evaluation, suggested that capnography was associated with higher survival rates but at an additional cost.

In the remaining adult populations, the clinical review found an increased detection of misplaced ETT tubes in adult trauma patients who underwent pre-hospital intubation attempts, and increased detection of respiratory events in patients recovering from orthopedic surgery. These results, however, are based on single studies — each contending with significant sources of biases that could have influenced their results. Due to the limited clinical evidence, the economic analysis was exploratory, based on the assumption that relative treatment effects would be consistent with what was observed in patients undergoing procedural sedation. The exploratory analyses suggested that capnography was the dominant intervention for adult patients in serious or critical condition and in post-operative care. These results, however, need to be interpreted with caution, given the limited clinical data.

The clinical and economic evidence for the use of capnography in pediatric patient populations was limited. For pediatric patients undergoing procedural sedation, there were no observed differences in clinical outcomes between capnography and standard monitoring. One study looking at the effectiveness of an immediate capnography signal, versus a delayed capnography signal, suggested that an immediate capnography signal was associated with a reduction in the number of hypoxemia events detected. Based on the clinical evidence for

capnography compared with standard monitoring, the economic analysis found that capnography was not cost-effective in pediatric patients undergoing procedural sedation. There was no evidence to assess the clinical effectiveness or cost-effectiveness of capnography for pediatric patients undergoing CPR or in post-operative care. For pediatric patients in serious or critical condition, the evidence captured in the clinical review assessed the use of capnography in the neonatal ICU; however, there was insufficient evidence to make any conclusions about the effectiveness of capnography in this population. The cost-effectiveness of capnography for use as a continuous monitor in this population is unknown.

There was no evidence to suggest a difference in harms outcomes with the use of capnography compared with no monitoring or standard monitoring in any population of interest in this review; however, further research should assess the impact of the occurrence of false-positive signals. Consideration of the barriers and supports of capnography across hospital and pre-hospital settings may facilitate the successful implementation of capnography devices. A lack of training and a lack of knowledge of capnography outputs and how to interpret the data to change the course of patient treatment may lead to lower adoption rates. If the technology and components are easily accessible, always available, and protocols for their use are in place, the likelihood of achieving successful implementation will be greater.

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APPENDIX 1: Literature Search Strategy

OVERVIEW	Capnography/Capnometry
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials Embase Ovid MEDLINE In-Process and Other Non-Indexed Citations Ovid MEDLINE Daily Ovid MEDLINE **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 31, 2015
Alerts:	Monthly search updates began July 31, 2015 and ran until March 14, 2016.
Study Types:	All study types included.
Limits:	January 1, 2005 to July 31, 2015 Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.kw	Keyword headings
.pt	Publication type
.dv	Device trade name
pmez	Ovid database code; MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cctr	EBM Reviews - Cochrane Central Register of Controlled Trials Embase

MULTI-DATABASE SEARCH STRATEGY (Capnography)	
#	**Searches**
1	Capnography/
2	capnometry/ use oemezd
3	capnograph/ use oemezd
4	(capnograph* or capnogram*).ti,ab,kw.
5	(Capnocheck or Waveline or "Echo CO2" or Ohmed Capnomac or Tidalwave or Spectra Ag5 or nGenuity or Dinamap MPS or Omni Express or Capnostream or Microcap or Nellcore or EMMA or Capnostat or Ultraview or Microstream).dv.

MULTI-DATABASE SEARCH STRATEGY (Capnography)	
6	or/1-5
7	6 not conference abstract.pt.
8	limit 7 to English language
9	limit 8 to yr="2005 -Current"
10	remove duplicates from 9
11	10 use pmez
12	10 use oemezd
13	10 use cctr

OVERVIEW	Carbon dioxide monitoring
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials Embase Ovid MEDLINE In-Process and Other Non-Indexed Citations Ovid MEDLINE Daily Ovid MEDLINE **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 12, 2015
Alerts:	Monthly search updates began August 12, 2015 and ran until March 14, 2016.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials.
Limits:	January 1, 2005 to August 12, 2015 Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.kw	Keyword headings
.pt	Publication type
.dv	Device trade name
pmez	Ovid database code; MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cctr	EBM Reviews - Cochrane Central Register of Controlled Trials Embase

MULTI-DATABASE SEARCH STRATEGY (Carbon dioxide monitoring)	
#	**Searches**
1	exp *Monitoring, Physiologic/ use pmez

MULTI-DATABASE SEARCH STRATEGY (Carbon dioxide monitoring)	
2	*physiologic monitoring/ use oemezd
3	(monitor* or record* or measure* or measuring or detect*).ti.
4	or/1-3
5	(end tidal or endtidal).ti,ab.
6	*Carbon Dioxide/
7	(CO2 or "CO 2" or carbon dioxide or ETCO2 or "ETCO 2" or "EtCO(2)" or PETCO2).ti,ab.
8	or/5-7
9	4 and 8
10	exp Cardiopulmonary Resuscitation/ or Heart Arrest/ or Heart Massage/ or exp Respiration, Artificial/ or exp Respiratory Insufficiency/
11	10 use pmez
12	*resuscitation/ or Heart Arrest/ or *heart massage/ or *artificial ventilation/ or exp *respiratory failure/
13	12 use oemezd
14	((Cardiopulmonary or cardio pulmonary or Cardiac or Heart or Coronary or Cardiovascular or cardio vascular or "mouth to mouth" or emergenc*) adj3 (Resuscitat* or life support)).ti,ab.
15	(code blue or CPR).ti,ab.
16	or/14-15
17	11 or 13 or 16
18	exp "Anesthesia and Analgesia"/ or exp Anesthesiology/ or exp Specialties, Surgical/ or exp Surgical Procedures, Operative/
19	18 use pmez
20	exp *anesthesia/ or *anesthesiology/ or exp *surgery/
21	20 use oemezd
22	(Anesthes* or anaesthes* or anesthet* or anaesthet* or analges* or sedation or sedate* or sedating or sedative* or surgery or surgical).ti,ab.
23	19 or 21 or 22
24	Critical Illness/ or exp Intensive Care Units/ or exp Critical Care/ or exp Emergency Service, Hospital/
25	24 use pmez
26	*critical illness/ or exp *intensive care/ or exp *emergency care/
27	26 use oemezd
28	((serious* or critical* or "life threatening") adj3 (condition* or illness* or ill)).ti,ab.
29	(Ventilat* or (artificial adj3 respirat*)).ti,ab.
30	((critical or intensive or trauma) adj3 care).ti,ab.
31	trauma patient*.ti,ab.
32	or/28-31
33	25 or 27 or 32
34	exp *Apnea/
35	exp *sleep disordered breathing/ use oemezd
36	(apnea* or apnoea* or hypopnea* or hypopnoea* or apneic-hypopneic or apnoeic-hypopnoeic).ti,ab.
37	((disordered or slow or shallow) adj3 (breathing* or respiration*)).ti,ab.
38	or/34-37
39	exp Analgesics, Opioid/ use pmez
40	*opiate/ use oemezd
41	(Opioid or opioids or narcotic* or opiate* or opium or buprenorphin* or buprenorfin* or buprenorphin* or buprenex or prefin or subutex or temgesic or buprex or butrans or probuphin* or probuphenin* or Brospina or Bupralex or Bupren or Buprine or Dorfene or Norphin or "Norspan Patch" or Pentorel or Shumeifen or

MULTI-DATABASE SEARCH STRATEGY (Carbon dioxide monitoring)	
	Sovenor or Subutex or Tidigesic or Transtec or suboxone or buprenorphine-naloxone or naloxone-buprenorphine or (buprenorphin* and naloxone) or zubsolv or bunavail or Codein* or Actacode or "Tylenol 3" or "Tylenol 4" or "Tylenol no 3" or "Tylenol no 4" or "Tylenol no 2" or "Tylenol no 3" or Emtec or Lenoltec or Triatec or Mersyndol or Fioricet or Ascomp or Tencal or Ambenyl or Bromanyl or BenzaClin or Brontex or codimal or Isocodeine or Ardinex or cocodamol or Panadiene or Paralgin or Solpadeine or Taluosil or Citodon or codaprin or Phenylhistine or Tricode or Allfen or Codal or Iophen or codicept or coducept or zapain or co-codamol or Efferalgan-codeine or migraeflux-green or Panadeine Forte or Methylmorphine or Fentanyl or phentanyl or fentanest or sublimaze or duragesic or durogesic or fentora or fentanyl* or matrifen or sentonil or sublimase or subsys or abstral or onsolis or pentanyl or sentonil or Actiq or Lazanda or Breakyl or Denpax or Dolforin or Effentora or Fantamax or Fencino or Fentadur or Fentalis or Fentamax or Fentanila or Fentanilo or Fentax or Filtaten or Instanyl or Ionsys or Leptanal or Mezolar Matrix or Opiodur or Osmanil or PecFent or Recivit or trofentyl or Victanyl or hydrocodon* or dihydrocodeinone or dicodid or robidone or hydrocon* or codinovo or hycodan or hycon or bekadid or hidrocodon* or multacodin or tussionex or vicoprofen or tussigon or Vicodin* or hydromorphon* or hydromorfinon or dihydromorphin* or palladone or dilaudid or dimorphone or hidromorfona or hydromorfon* or idromorfone or laudacon or novolaudon Meperidin* or Pethidine or Meperidol or Pipersal or Pethanol or Methadon* or Morphin* or Morphium or oxycodone* or oxycone or dinarkon or kihydrone or Targin or oxyneo or Tramadol or Pentazocine or Alfentanil or Alfenta or Alphaprodine or Butorphanol or Dextromoramide or Dextropropoxyphene or Enkephalin or Ethylketocyclazocine or Ethylmorphine or Etorphine or Heroin or Levorphanol or Meptazinol or Methadyl Acetate or Nalbuphine or Oxymorphone or Opana or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Sufentanil or Sufenta or Tilidine).ti,ab.
42	or/39-41
43	exp Postoperative Period/ or postoperative complications/ or "delayed emergence from anesthesia"/ or pain, postoperative/
44	43 use pmez
45	exp *postoperative period/ or *postoperative pain/ or *postoperative complication/
46	45 use oemezd
47	(postoperative or postoperatively or postanesthesia or postanaesthesia).ti,ab.
48	(post adj3 (operative or operatively or anesthesia or anaesthesia or surgery or surgeries or surgical or operating* or operation* or procedural or procedure)).ti,ab.
49	(anesthesia adj3 recovery).ti,ab.
50	or/47-49
51	44 or 46 or 50
52	17 or 23 or 33 or 38 or 42 or 51
53	meta-analysis.pt.
54	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
55	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
56	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
57	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
58	(data synthes* or data extraction* or data abstraction*).ti,ab.
59	(handsearch* or hand search*).ti,ab.
60	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
61	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
62	(meta regression* or metaregression*).ti,ab.
63	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
64	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
65	(cochrane or (health adj2 technology assessment) or evidence report).jw.

MULTI-DATABASE SEARCH STRATEGY (Carbon dioxide monitoring)	
66	(meta-analysis or systematic review).md.
67	(comparative adj3 (efficacy or effectiveness)).ti,ab.
68	(outcomes research or relative effectiveness).ti,ab.
69	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
70	or/53-69
71	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
72	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
73	Multicenter Study.pt.
74	Randomized Controlled Trial/
75	Randomized Controlled Trials as Topic/
76	"Randomized Controlled Trial (topic)"/
77	Controlled Clinical Trial/
78	Controlled Clinical Trials as Topic/
79	"Controlled Clinical Trial (topic)"/
80	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
81	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
82	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
83	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
84	Randomization/
85	Random Allocation/
86	Double-Blind Method/
87	Double-Blind Procedure/
88	Double-Blind Studies/
89	Single-Blind Method/
90	Single Blind Procedure/
91	Single-Blind Studies/
92	Placebos/
93	Placebo/
94	Control Groups/
95	Control Group/
96	Cross-Over Studies/ or Crossover Procedure/
97	(random* or sham or placebo*).ti,ab,hw.
98	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
99	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
100	(control* adj3 (study or studies or trial*)).ti,ab,hw.
101	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
102	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
103	(phase adj3 (study or studies or trial*)).ti,ab,hw.
104	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
105	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
106	allocated.ti,ab,hw.
107	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
108	trial.ti.

MULTI-DATABASE SEARCH STRATEGY (Carbon dioxide monitoring)	
109	or/71-108
110	exp animals/
111	exp animal experimentation/
112	exp models animal/
113	exp animal experiment/
114	nonhuman/
115	exp vertebrate/
116	animal.po.
117	or/110-116
118	exp humans/
119	exp human experiment/
120	human.po.
121	or/118-120
122	117 not 121
123	9 and (52 or 70 or 109)
124	123 not 122
125	124 not conference abstract.pt.
126	Capnography/
127	capnometry/ use oemezd
128	capnograph/ use oemezd
129	(capnograph* or capnogram*).ti,ab,kw.
130	(Capnocheck or Waveline or "Echo CO2" or Ohmed Capnomac or Tidalwave or Spectra Ag5 or nGenuity or Dinamap MPS or Omni Express or Capnostream or Microcap or Nellcore or EMMA or Capnostat or Ultraview or Microstream).dv.
131	or/126-130
132	125 not 131
133	limit 132 to English language
134	limit 133 to yr="2005 -Current"
135	remove duplicates from 134

OVERVIEW	Economic search
Interface:	Ovid
Databases:	Embase Ovid MEDLINE In-Process and Other Non-Indexed Citations Ovid MEDLINE Daily Ovid MEDLINE **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 25, 2015
Alerts:	Monthly search updates began September 25, 2015 and ran until March 14, 2016.
Study Types:	Cost analysis studies, quality of life studies, and economic literature.
Limits:	January 1, 2005 to September 25, 2015 Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.kw	Keyword headings
.pt	Publication type
.dv	Device trade name
pmez	Ovid database code; MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
1	Capnography/
2	capnometry/ use oemezd
3	capnograph/ use oemezd
4	(capnograph* or capnogram*).ti,ab,kw.
5	(Capnocheck or Waveline or "Echo CO2" or Ohmed Capnomac or Tidalwave or Spectra Ag5 or nGenuity or Dinamap MPS or Omni Express or Capnostream or Microcap or Nellcore or EMMA or Capnostat or Ultraview or Microstream).dv.
6	capnomet*.ti,ab,kw.
7	or/1-6
8	exp *Monitoring, Physiologic/ use pmez
9	*physiologic monitoring/ use oemezd
10	(monitor* or record* or measure* or measuring or detect*).ti.
11	or/8-10
12	(end tidal or endtidal).ti,ab.
13	*Carbon Dioxide/
14	(CO2 or "CO 2" or carbon dioxide or ETCO2 or "ETCO 2" or "EtCO(2)" or PETCO2).ti,ab.
15	or/12-14
16	11 and 15
17	exp Cardiopulmonary Resuscitation/ or Heart Arrest/ or Heart Massage/ or exp Respiration, Artificial/ or exp Respiratory Insufficiency/
18	17 use pmez
19	*resuscitation/ or Heart Arrest/ or *heart massage/ or *artificial ventilation/ or exp *respiratory failure/
20	19 use oemezd
21	((Cardiopulmonary or cardio pulmonary or Cardiac or Heart or Coronary or Cardiovascular or cardio vascular or "mouth to mouth" or emergenc*) adj3 (Resuscitat* or life support)).ti,ab.
22	(code blue or CPR).ti,ab.
23	or/21-22
24	18 or 20 or 23

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
25	exp "Anesthesia and Analgesia"/ or exp Anesthesiology/ or exp Specialties, Surgical/ or exp Surgical Procedures, Operative/
26	25 use pmez
27	exp *anesthesia/ or *anesthesiology/ or exp *surgery/
28	27 use oemezd
29	(Anesthes* or anaesthes* or anesthet* or anaesthet* or analges* or sedation or sedate* or sedating or sedative* or surgery or surgical).ti,ab.
30	26 or 28 or 29
31	Critical Illness/ or exp Intensive Care Units/ or exp Critical Care/ or exp Emergency Service, Hospital/
32	31 use pmez
33	*critical illness/ or exp *intensive care/ or exp *emergency care/
34	33 use oemezd
35	((serious* or critical* or "life threatening") adj3 (condition* or illness* or ill)).ti,ab.
36	(Ventilat* or (artificial adj3 respirat*)).ti,ab.
37	((critical or intensive or trauma) adj3 care).ti,ab.
38	trauma patient*.ti,ab.
39	or/35-38
40	32 or 34 or 39
41	exp *Apnea/
42	exp *sleep disordered breathing/ use oemezd
43	(apnea* or apnoea* or hypopnea* or hypopnoea* or apneic-hypopneic or apnoeic-hypopnoeic).ti,ab.
44	((disordered or slow or shallow) adj3 (breathing* or respiration*)).ti,ab.
45	or/41-44
46	exp Analgesics, Opioid/ use pmez
47	*opiate/ use oemezd
48	(Opioid or opioids or narcotic* or opiate* or opium or buprenorphin* or buprenorfin* or buprenorphin* or buprenex or prefin or subutex or temgesic or buprex or butrans or probuphin* or probuphenin* or Brospina or Bupralex or Bupren or Buprine or Dorfene or Norphin or "Norspan Patch" or Pentorel or Shumeifen or Sovenor or Subutex or Tidigesic or Transtec or suboxone or buprenorphine-naloxone or naloxone-buprenorphine or (buprenorphin* and naloxone) or zubsolv or bunavail or Codein* or Actacode or "Tylenol 3" or "Tylenol 4" or "Tylenol no 3" or "Tylenol no 4" or "Tylenol no 2" or "Tylenol no 3" or Emtec or Lenoltec or Triatec or Mersyndol or Fioricet or Ascomp or Tencal or Ambenyl or Bromanyl or BenzaClin or Brontex or codimal or Isocodeine or Ardinex or cocodamol or Panadiene or Paralgin or Solpadeine or Taluosil or Citodon or codaprin or Phenylhistine or Tricode or Allfen or Codal or Iophen or codicept or coducept or zapain or co-codamol or Efferalgan-codeine or migraeflux-green or Panadeine Forte or Methylmorphine or Fentanyl or phentanyl or fentanest or sublimaze or duragesic or durogesic or fentora or fentanyl* or matrifen or sentonil or sublimase or subsys or abstral or onsolis or pentanyl or sentonil or Actiq or Lazanda or Breakyl or Denpax or Dolforin or Effentora or Fantamax or Fencino or Fentadur or Fentalis or Fentamax or Fentanila or Fentanilo or Fentax or Filtaten or Instanyl or Ionsys or Leptanal or Mezolar Matrix or Opiodur or Osmanil or PecFent or Recivit or trofentyl or Victanyl or hydrocodon* or dihydrocodeinone or dicodid or robidone or hydrocon* or codinovo or hycodan or hycon or bekadid or hidrocodon* or multacodin or tussionex or vicoprofen or tussigon or Vicodin* or hydromorphon* or hydromorfinon or dihydromorphin* or palladone or dilaudid or dimorphone or hidromorfona or hydromorfon* or idromorfone or laudacon or novolaudon Meperidin* or Pethidine or Meperidol or Pipersal or Pethanol or Methadon* or Morphin* or Morphium or oxycodone* or oxycone or dinarkon or kihydrone or Targin or oxyneo or Tramadol or Pentazocine or Alfentanil or Alfenta or Alphaprodine or Butorphanol or Dextromoramide or Dextropropoxyphene or Enkephalin or Ethylketocyclazocine or Ethylmorphine or Etorphine or Heroin or Levorphanol or Meptazinol or Methadyl Acetate or Nalbuphine or Oxymorphone or Opana or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Sufentanil or Sufenta or Tilidine).ti,ab.
49	or/46-48

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
50	exp Postoperative Period/ or postoperative complications/ or "delayed emergence from anesthesia"/ or pain, postoperative/
51	50 use pmez
52	exp *postoperative period/ or *postoperative pain/ or *postoperative complication/
53	52 use oemezd
54	(postoperative or postoperatively or postanesthesia or postanaesthesia).ti,ab.
55	(post adj3 (operative or operatively or anesthesia or anaesthesia or surgery or surgeries or surgical or operating* or operation* or procedural or procedure)).ti,ab.
56	(anesthesia adj3 recovery).ti,ab.
57	or/54-56
58	51 or 53 or 57
59	(45 or 49) and 58
60	24 or 30 or 40 or 45 or 49 or 58
61	16 and 60
62	7 or 61
63	*economics/
64	exp *"costs and cost analysis"/
65	(economic adj2 model*).mp.
66	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
67	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti.
68	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
69	(cost or economic*).ti. and (costs or cost-effectiveness or markov).ab.
70	or/63-69
71	62 and 70
72	Economics/
73	exp "Costs and Cost Analysis"/
74	Economics, Nursing/
75	Economics, Medical/
76	Economics, Pharmaceutical/
77	exp Economics, Hospital/
78	Economics, Dental/
79	exp "Fees and Charges"/
80	exp Budgets/
81	budget*.ti,ab.
82	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.
83	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
84	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.
85	(value adj2 (money or monetary)).ti,ab.
86	exp models, economic/
87	economic model*.ti,ab.

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
88	markov chains/
89	markov.ti,ab.
90	monte carlo method/
91	monte carlo.ti,ab.
92	exp Decision Theory/
93	(decision* adj2 (tree* or analy* or model*)).ti,ab.
94	or/72-93
95	94 use pmez
96	62 and 95
97	Economics/
98	Cost/
99	exp Health Economics/
100	Budget/
101	budget*.ti,ab.
102	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.
103	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
104	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.
105	(value adj2 (money or monetary)).ti,ab.
106	Statistical Model/
107	economic model*.ti,ab.
108	Probability/
109	markov.ti,ab.
110	monte carlo method/
111	monte carlo.ti,ab.
112	Decision Theory/
113	Decision Tree/
114	(decision* adj2 (tree* or analy* or model*)).ti,ab.
115	or/97-114
116	115 use oemezd
117	62 and 116
118	"Value of Life"/
119	Quality of Life/
120	quality of life.ti.
121	((instrument or instruments) adj3 quality of life).ab.
122	Quality-Adjusted Life Years/
123	quality adjusted life.ti,ab.
124	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
125	disability adjusted life.ti,ab.
126	daly*.ti,ab.
127	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
128	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
129	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
130	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
131	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
132	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
133	(hye or hyes).ti,ab.
134	(health* adj2 year* adj2 equivalent*).ti,ab.
135	(pqol or qls).ti,ab.
136	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
137	nottingham health profile*.ti,ab.
138	sickness impact profile.ti,ab.
139	exp health status indicators/
140	(health adj3 (utilit* or status)).ti,ab.
141	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
142	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
143	disutilit*.ti,ab.
144	rosser.ti,ab.
145	willingness to pay.ti,ab.
146	standard gamble*.ti,ab.
147	(time trade off or time tradeoff).ti,ab.
148	tto.ti,ab.
149	(hui or hui1 or hui2 or hui3).ti,ab.
150	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
151	duke health profile.ti,ab.
152	functional status questionnaire.ti,ab.
153	dartmouth coop functional health assessment*.ti,ab.
154	or/118-153
155	154 use pmez
156	62 and 155
157	socioeconomics/
158	exp Quality of Life/
159	quality of life.ti.
160	((instrument or instruments) adj3 quality of life).ab.
161	Quality-Adjusted Life Year/
162	quality adjusted life.ti,ab.
163	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
164	disability adjusted life.ti,ab.
165	daly*.ti,ab.
166	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
167	(sf6 or sf 6 or short form 6 or shortform 6 or sf6d or sf 6d or short form 6d or shortform 6d or sf six or sfsix

MULTI-DATABASE SEARCH STRATEGY (Economics)	
#	**Searches**
	or shortform six or short form six).ti,ab.
168	(sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.
169	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
170	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
171	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
172	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
173	(hye or hyes).ti,ab.
174	(health* adj2 year* adj2 equivalent*).ti,ab.
175	(pqol or qls).ti,ab.
176	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
177	nottingham health profile*.ti,ab.
178	nottingham health profile/
179	sickness impact profile.ti,ab.
180	sickness impact profile/
181	health status indicator/
182	(health adj3 (utilit* or status)).ti,ab.
183	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
184	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
185	disutilit*.ti,ab.
186	rosser.ti,ab.
187	willingness to pay.ti,ab.
188	standard gamble*.ti,ab.
189	(time trade off or time tradeoff).ti,ab.
190	tto.ti,ab.
191	(hui or hui1 or hui2 or hui3).ti,ab.
192	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
193	duke health profile.ti,ab.
194	functional status questionnaire.ti,ab.
195	dartmouth coop functional health assessment*.ti,ab.
196	or/157-195
197	196 use oemezd
198	62 and 197
199	71 or 96 or 117 or 156 or 198
200	limit 199 to English language
201	limit 200 to yr="2005 -Current"
202	remove duplicates from 201

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 7, 2015	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	July to August 2015
Keywords:	Capnography, capnometry, ETCO2, carbon dioxide monitoring
Limits:	2005 to 2015

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (www.cadth.ca/grey-matters), were searched:

- Advisories and Warnings
- Advocacy group, association
- Background
- Clinical Practice Guidelines
- Clinical Trial Listing
- Databases (free)
- Health Economics
- Health Technology Assessment Agencies
- Internet Search
- Open Access Journals
- Regulatory Approvals.

APPENDIX 2: Detailed Methods and Results of the Review of Economic studies

Methods

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records and daily updates via Ovid; Embase via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were capnography, capnometry, and carbon dioxide monitoring of patients undergoing CPR, procedural sedation, in serious or critical condition, with obstructive sleep apnea, or receiving high opioid doses post-operatively.

Methodological filters were applied to limit retrieval to economic studies. Retrieval was limited to English language documents published between January 1, 2005 and September 25, 2015. See APPENDIX 1: Literature Search Strategy for the detailed search strategies. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/grey-matters), which includes the websites of health technology assessment agencies and other economics-related resources. Google and other Internet search engines were used to search for additional Web-based materials, including conference abstracts. These searches were supplemented through contacts with appropriate experts and industry. See APPENDIX 1: Literature Search Strategy for more information on the grey literature search strategy.

Selection Criteria

Inclusion criteria: Studies were eligible for inclusion in the systematic review if they met the criteria listed in APPENDIX 1: Literature Search Strategy.

Table 12: Inclusion Criteria for the Economic Review

	Research Questions 1 and 2	Research Questions 3 and 4	Research Questions 5 and 6	Research Questions 7 and 8
Population	Adult (aged ≥ 18 years) and pediatric patients who are sedated for the purposes of tolerating an interventional or diagnostic procedure.	Adult (aged ≥ 18 years) and pediatric patients who are experiencing cardiac arrest and/or absent or abnormal breathing for which CPR is being performed.	Adult (aged ≥ 18 years) and pediatric patients who are in serious or critical condition where vital signs are either unstable or may be unstable and are not within normal limits.	Adult (aged ≥ 18 years) and pediatric patients receiving post-operative care with known obstructive sleep apnea and/or who are receiving high opioid doses.
Intervention	$ETCO_2$ monitoring using capnography (alone or in combination with other monitoring equipment)			
Comparators	• No $ETCO_2$ monitoring			

	Research Questions 1 and 2	Research Questions 3 and 4	Research Questions 5 and 6	Research Questions 7 and 8
	• Standard monitoring (e.g., pulse oximetry, pulse rate, blood pressure, visual assessment) • Capnography (comparing between alternative types, such as fixed or portable) • Capnometry • Exhaled CO_2 detector • Esophageal detector device (for patients who are intubated)			
Outcomes	• ICER: cost per unit of clinical outcome; cost per QALYs • Costs			
Study Setting	In hospital	In hospital or pre-hospital settings[a]		In hospital
Study Design	Health technology assessment reports and economic evaluation studies (cost analysis, cost-consequence analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)			

CO_2 = carbon dioxide; CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
[a] Pre-hospital settings include care provided by health care providers as first responders and during ambulatory transport.

Exclusion Criteria: Studies were excluded if they did not include a defined population or condition or they were not published in English. Duplicate publications, abstracts, summaries, case studies, reviews, comments, letters, and editorials were also excluded.

Selection Method: Two reviewers used the screening checklist in Table 13 to review the title and abstract of each citation. Full-text articles were obtained for citations that could not be excluded by title and abstract screening, and the full-text was assessed using explicit predetermined criteria (Table 14). Disagreements between reviewers were resolved by consensus, consulting a third reviewer when necessary.

Table 13: Title and Abstract Screening Checklist for the Review of Economic Studies

Ref #:	
Author:	
Population	Pediatric and adult
Intervention	$ETCO_2$ monitoring using capnography (alone or in combination with other monitoring equipment)
Comparator	Standard monitoring
Outcome	ICER: cost per unit of outcome; cost per QALYs Other
Study type	Health technology assessment reports and economic evaluation studies (cost analysis, cost-consequence analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)

$ETCO_2$ = end-tidal carbon dioxide; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 14: Full-Text Screening Checklist for the Review of Economic Studies

Ref #:		
Author:		
Year:		
	Include	**Exclude**
Population	Adult (aged ≥ 18 years) and pediatric patients: - who are sedated for the purposes of tolerating an interventional or diagnostic procedure; - who are experiencing cardiac arrest and/or absent or abnormal breathing for which CPR is being performed; - who are in serious or critical condition where vital signs are either unstable or may be unstable and are not within normal limits; or - who are receiving post-operative care with known obstructive sleep apnea and/or who are receiving high opioid doses.	Studies did not include a defined population
Intervention	$ETCO_2$ monitoring using capnography (alone or in combination with other monitoring equipment)	Studies did not include a defined intervention
Comparator	– No $ETCO_2$ monitoring – Standard monitoring (e.g., pulse oximetry, pulse rate, blood pressure, visual assessment) – Capnography (comparing between alternative types, such as fixed or portable) – Capnometry – Exhaled CO_2 detector – Esophageal detector device (for patients who are intubated)	Studies did not include a defined comparator
Outcome	ICER: cost per unit of outcome; cost per QALYs Other	
Study type	Health technology assessment reports and economic evaluation studies (cost analysis, cost consequence analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)	Abstracts/ summaries, case studies, reviews, comments, letters, and editorials

CO2 = carbon dioxide; CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Data Extraction

One reviewer used a standard data extraction form to record relevant information, which was verified by a second reviewer. The information collected include author, title, country, objective, population, setting, comparators, form of economic analysis, perspective, timeframe, clinical effectiveness data source, health and cost outcomes, data and decision modelling details, sensitivity analysis approach, currency and year, results from the marginal analysis, and conclusion.

Strategy for Quality Assessment of the Studies

The quality of each included study was independently assessed by two reviewers with the Drummond checklist.[146] Disagreements between reviewers were resolved by consensus, consulting a third reviewer when necessary.

Results

Quantity of Research Available

Of the 210 citations identified from the economic search, 20 were identified for further review. A total of 19 articles were excluded, resulting in one study that met the selection criteria

(kappa = 1). Figure 4 shows the PRISMA flowchart of the process used to identify and select studies for the review, as well as the main reasons for exclusion. Table 15 presents the list of excluded studies and the reasons for exclusion. The details of the included study are described in Table 16.

Study Characteristics
One costing study[79] was identified that evaluated the utilization of blood gases before and after the implementation of standard continuous sidestream capnography on all mechanically ventilated pediatric patients in serious or critical condition. This was a US-based retrospective review of a quality improvement project.

Quality Assessment
The Drummond checklist[146] was used to critically appraise the one economic evaluation[79] identified. Based on the checklist, there were some deficiencies in the study design and reporting. For instance, the perspective of the analysis was not justified and it is therefore difficult to assess whether all relevant costs were considered as only blood gas charges were factored. Despite mentioning the acquisition costs of the capnography devices, these costs were not included in the analysis. The model time horizon was not stated further, making it difficult to assess whether all relevant costs and effects of monitoring were considered. Similarly, no justification of the form of the economic evaluation was explicitly stated, and this may explain why an incremental analysis was not performed to address the trade-offs between the treatment strategies. The authors did not undertake any sensitivity analysis as part of the analysis of the results.

Summary of Results
Rowan et al.[79] compared the utilization of blood gases before and after the implementation of standard continuous capnography in the pediatric intensive care unit. They compared data from April to September 2009 and April to September 2010 (before the initiation of capnography) to data collected from April to September 2011 (after the initiation of capnography).

The results showed that there was a statistically significant decrease in the total number of blood gases analyzed, average number of blood gases analyzed per patient, and average number of blood gases analyzed per ventilator day after the institution of continuous $ETCO_2$ monitoring, compared with the same time period from the previous two years. The results also identified that the total blood gas charge decreased from $2,207,804 in 2009 and $2,261,051 in 2010 to $1,544,360 in 2011; a total savings over a six-month period of $768,796.

Rowan et al.[79] reported a number of limitations to their study. For example, they were unable to determine retrospectively why a blood gas was ordered. The authors also noted that a decrease in the utilization of blood gases may lead to other areas of improvement for quality, safety, and costs. However, they did not evaluate decreases in the amount of times the central or arterial line was accessed, reduction in catheter-related infections, mortality rate, iatrogenic anemia, and their associated cost savings.

The authors concluded that continuous capnography resulted in a significant savings over a six-month period by decreasing the utilization of blood gas measurements.

Figure 4: Study Selection Flow Diagram — Economic Review

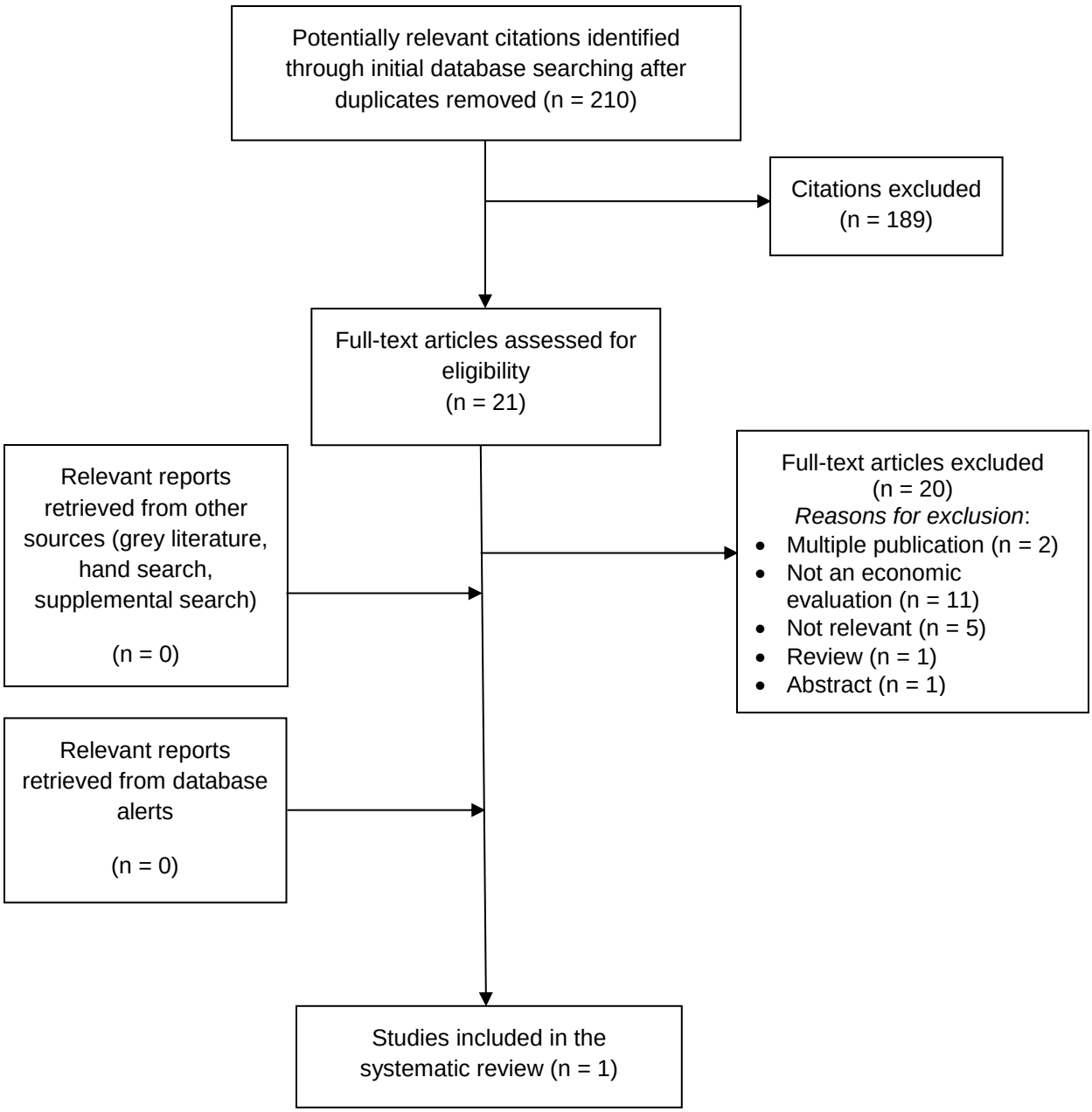


Table 15: List of Excluded Studies From the Review of Economic Studies

Study	Reasons for Exclusion
Boyd P. Revenue generation model screening for OSA during hospitalizations commonly monitored with capnography [abstract]. Sleep Conference: 24th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP 2010 San Antonio, TX United States	Not relevant Abstract
Bradley BD, Green G, Ramsay T, Seely AJ. Impact of sedation and organ failure on continuous heart and respiratory rate variability monitoring in critically ill patients: a pilot study. Crit Care Med. 2013 Feb;41(2):433-44	Not an economic evaluation
Conway A, Page K, Rolley JX, Worrall-Carter L. Nurse-administered procedural sedation and analgesia in the cardiac catheter laboratory: an integrative review. Int J Nurs Stud. 2011 Aug; 48(8):1012-23.	Review (clinical studies)
Curtin A, Izzetoglu K, Reynolds J, Menon R, Izzetoglu M, Osbakken M, et al. Functional near-infrared spectroscopy for the measurement of propofol effects in conscious sedation during outpatient elective colonoscopy. Neuroimage. 2014 Jan 15;85 Pt 1:626-36, 2014 Jan 15.:-36	Not an economic evaluation
Dewitt J, McGreevy K, Sherman S, Imperiale TF. Nurse-administered propofol sedation compared with midazolam and meperidine for EUS: a prospective, randomized trial. Gastrointest Endosc. 2008 Sep; 68(3):499-509.	Not relevant
Dziewas R, Hopmann B, Humpert M, Bontert M, Dittrich R, Ludemann P, et al. Capnography screening for sleep apnea in patients with acute stroke. Neurol Res. 2005 Jan; 27(1):83-7.	Not an economic evaluation
Green GC, Bradley B, Bravi A, Seely AJ. Continuous multiorgan variability analysis to track severity of organ failure in critically ill patients. J Crit Care. 2013 Oct; 28(5):879-11.	Not an economic evaluation
Herbert LJ, Wilson IH. Pulse oximetry in low-resource settings. Breathe. 2012; 9(2):90-7.	Not an economic evaluation
Johnson A, Schweitzer D, Ahrens T. Time to throw away your stethoscope? Capnography: Evidence-based patient monitoring technology. J Radiol Nurs. 2011; 30(1):25-34.	Not an economic evaluation
Jopling MW, Kofol T, Heard L. Evaluating the cost-effectiveness of capnography monitoring in procedural sedation: A gastroenterology (GI) suite cost-avoidance model [abstract]. Gastrointestinal Endoscopy Conference: Digestive Diease Week, DDW 2015 ASGE Washington, DC United States Conference	Abstract
Kochhar G, Mehta PP, Kirsh B, Rizk MK, Wang Y, John B, et al. Does capnography prevent hypoxemia in ASA 1-2 outpatients undergoing elective EGD targeting moderate sedation? Results from a prospective, randomized, single blinded study [abstract]. Gastroenterology Conference: Digestive Disease Week 2015, DDW 2015 Washington, DC United States	Not an economic evaluation Abstract
Martin M, Brown C, Bayard D, Demetriades D, Salim A, Gertz R, et al. Continuous noninvasive monitoring of cardiac performance and tissue perfusion in pediatric trauma patients. J Pediatr Surg. 2005 Dec; 40(12):1957-63.	Not an economic evaluation
Mehta P, Kochhar G, Albeldawi M, Kirsh B, Rizk M, Putka B, et al. Capnographic monitoring does not improve detection of hypoxemia in colonoscopy with moderate sedation: A randomized, controlled trial [abstract]. American Journal of Gastroenterology Conference: 79th Annual Scientific Meeting of the American College of Gastroenterology Philadelphia, PA United States	Not an economic evaluation Abstract
Negron-Gonzalez M, Cohen S, Lamba A, Hunter CW, McDonough C, Tse J. No-cost TSE "Mask" prevents severe desaturation and reduces risk of fire hazard in obese patients under moderatedeep propofol sedation during various lengthy surgical procedures [abstract]. Anesthesia and Analgesia Conference: 2011 Annual Meeting of the International Anesthesia Research Society, IARS 2011 Vancouver, BC Canada	Not relevant Abstract
Pasquina P, Farr P, Bourqui P, Bridevaux P-O, Janssens J-P. Home-based versus hospital-based monitoring of long-term home ventilation: A pilot study	Not relevant Abstract

Study	Reasons for Exclusion
[abstract]. Respiration Conference: Joint Annual Meeting of the Swiss Respiratory Society, Swiss Society of Oto-Rhino-Laryngology, Head and Neck Surgery, Swiss Paediatric Respiratory Society, Swiss Society for Thoracic Surgery 2011 Interlaken Switzerland	
Rowan C, Ahmed S, Hedlund T, Speicher R. Continuous capnography decreases the utilization of blood gases [abstract]. Critical Care Medicine Conference: Critical Care Congress 2012 Houston, TX United States	Duplication Abstract
* Saunders R, Erslon MG, Vargo J. Cost-Effectiveness of Capnography Monitoring During Gastrointestinal Endoscopy Targeting Moderate Sedation. Value Health. 2015 Nov; 18(7):A355.	Abstract
Shepherd J, Jones J, Frampton GK, Bryant J, Baxter L, Cooper K. Clinical effectiveness and cost-effectiveness of depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend): A systematic review and economic evaluation. Health Technol Assess. 2013; 17(34):1-264.	Not relevant
Smally AJ, Nowicki TA. Sedation in the emergency department. Curr Opin Anaesthesiol. 2007; 20(4):379-83.	Not an economic evaluation
Tan HL, Kheirandish-Gozal L, Gozal D. Pediatric Home Sleep Apnea Testing: Slowly Getting There! Chest. 2015 Aug 13.	Not an economic evaluation
Tse J, Negron-Gonzalez M, Razvi B, Denny JT, Mellender S, Cohen S. Pre-oxygenation with no-cost TSE "Mask" prevents severe desaturation and improves oxygenation in obese patients under deep propofol sedation during lengthy upper GI endoscopy [abstract]. Anesthesia and Analgesia Conference: 2011 Annual Meeting of the International Anesthesia Research Society, IARS 2011 Vancouver, BC Canada	Duplication Not relevant Abstract

Table 16: Description of the Included Study in the Review of Economic Studies

Study	Rowan et al. 2014[79]
Objective	To determine if implementation of continuous capnography monitoring decreases the utilization of blood gases resulting in decreased charges.
Population	Mechanically ventilated patients in the pediatric intensive care unit (patients from the cardiac critical care service who received $ETCO_2$ monitoring were excluded)
Setting	United States, retrospective review
Comparators	Before and after the implementation of continuous sidestream capnography (comparing the utilization of blood gases)
Form of economic analysis	Cost analysis
Perspective	Not stated
Timeframe	(1) April 2009 to September 2009 (before the implementation of capnography) (2) April 2010 to September 2010 (before the implementation of capnography) (3) April 2011 to September 2011 (after the implementation of capnography)
Clinical effectiveness data source	Total number of blood gas analyses, ventilator, and patient days were taken from a 3-year period US study (data collected from clinical decision support)
Quality of life	NA
Direct costs	Cost savings from decreased number of blood-gas analysis (data collected from hospital accounting)
Indirect costs	NA
Data modelling details	NA
Decision modelling details	NA
Sensitivity analysis approach	One-way ANOVA

Study	Rowan et al. 2014[79]
Currency and year	US 2010
Important findings from sensitivity analysis	There was a statistically significant decrease in the total number of blood gases analyzed, and in the average number of blood gases analyzed per patient and per ventilator day after the institution of continuous $ETCO_2$ monitoring, compared with the same time period from the prior years.
Results	The total charge savings over a 6-month period was $880,496.
Conclusions	Continuous capnography resulted in a significant savings over a 6-month period by decreasing the utilization of blood gas measurements.

ANOVA = analysis of variance; $ETCO_2$ = end-tidal carbon dioxide; NA = not applicable.

APPENDIX 3: Full-Text Screening Checklist

Reviewer: _____ **Date:** _____

Ref#: _____

Author: _____

Year: _____

Did the study include:	**Yes (include)**	**Unclear (include)**	**No (exclude)**
1) Patients under anesthesia and/or sedation *or* requiring CPR *or* who were in serious or critical condition *or* post-operatively in patients with known obstructive sleep apnea and/or receiving high opioid doses?	☐	☐	☐
2) $ETCO_2$ monitoring using a capnography device?	☐	☐	☐
3) Any of the following as the study outcomes? • Detection of respiratory failure (hypoxemia, hypercapnia) • Survival of acute event • Survival to hospital discharge • Morbidity (neurological, organ damage) • Detection of a respiratory event • Time to detection of a respiratory event • Hypoxia • Return of spontaneous circulation • Effectiveness of chest compressions • Change in clinical management • Length of hospital stay • Correct placement of endotracheal tube	☐	☐	☐
4) Any of the following study designs: • RCT • Non-RCT or observational study (e.g., quasi-experimental, cohort, case-control, controlled before and after)	☐	☐	☐
Decision for including the study in the review:	**Yes** ☐		**No** ☐
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No or inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Not primary report of study ☐ Study description only ☐ Other:_____		

CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; RCT = randomized controlled trial.

APPENDIX 4: Data Extraction Form — Clinical Review

Reviewer: _____ **Date:** _____

STUDY	
Ref ID	
Author	
Publication year	
Country	
Funding	

METHODOLOGY	
Study design	☐ RCT ☐ Non-randomized controlled trial ☐ Quasi-experimental study ☐ Controlled before-after study ☐ Cohort study ☐ Case-control study ☐ Other:_____
Indication	☐ Procedural sedation ☐ CPR ☐ Serious or critical condition ☐ Post-operative patients (with known obstructive sleep apnea and/or receiving high doses of opioids)
Study setting (e.g., urban, rural, or remote; hospital size; general hospital; teaching hospital; hospital department or suite)	
Eligibility criteria	
Key exclusion criteria	
Total sample size	
Number of withdrawals (reason)	
Provider of sedation or anesthesia	
Health care provider reading the capnography monitor (e.g., anesthesiologist, nurse)	
Provider experience (e.g., number of years)	

INTERVENTION OR COMPARATOR		
$ETCO_2$ device (check all that apply)	**Technical details of $ETCO_2$ device**	**Comparator (type and technical details)**
□ Sidestream □ Mainstream □ Fixed (i.e., modular or built into a multi-parameter monitoring device) □ Portable □ Not specified □ Other: _____		

REPORTED OUTCOMES	
Primary (including definition)	
Secondary (including definition)	

POPULATION CHARACTERISTICS		
	$ETCO_2$ Device	**Comparator**
Mean or median age, year (range)		
Gender (% female)		
BMI		
Smoking status		
Cardiovascular disease		
Respiratory disease (COPD, asthma)		
Sleep apnea		
Pulmonary embolus		
Mucus plugging		
Regular narcotic use		
Intubated (%)		
Research Questions 1 and 2 (procedural sedation)		
1. Procedure type 2. Procedure time (minutes) 3. Sedative type 4. Sedative dose 5. Sedation performed by (specialization) 6. Ramsay Sedation Scale score 7. ASA class Other: _____		
Research Questions 3 and 4 (CPR)		
1. Cause of arrest 2. Use of sedatives 3. Time since acute event Other: _____		

POPULATION CHARACTERISTICS		
Research Questions 5 and 6 (serious or critical condition)		
1. Reason for admission 2. Use of sedatives Other: _____		
Research Questions 7 and 8 (post-operative patients with known obstructive sleep apnea, and/or who are receiving high doses of opioids)		
1. Procedure type 2. Procedure length 3. Use of sedatives Obstructive sleep apnea: 4. Diagnosis of sleep apnea (years) 5. Severity of sleep apnea 6. Compliance with CPAP therapy High-dose opioid use: 7. Opioid type 8. Opioid dose 9. Use of other sedatives (e.g., benzodiazepines) 10. Pre-existing narcotic tolerance Other: _____		

RESULTS								
Outcome	**$ETCO_2$ Device**			**Comparator**			***P* value**	
Clinical Outcomes[a,b]								
Outcome 1: _____								
Outcome 2: _____								
Clinical Outcomes[b,c]	**N**	**#event**	**%**	**N**	**#event**	**%**	**RR or HR (95% CI)**	***P* Value**
Outcome 1: _____								
Outcome 2: _____								
Outcome 3: _____								

Did the article report any data relevant to other study questions? □ Yes: Q# _____ □ No

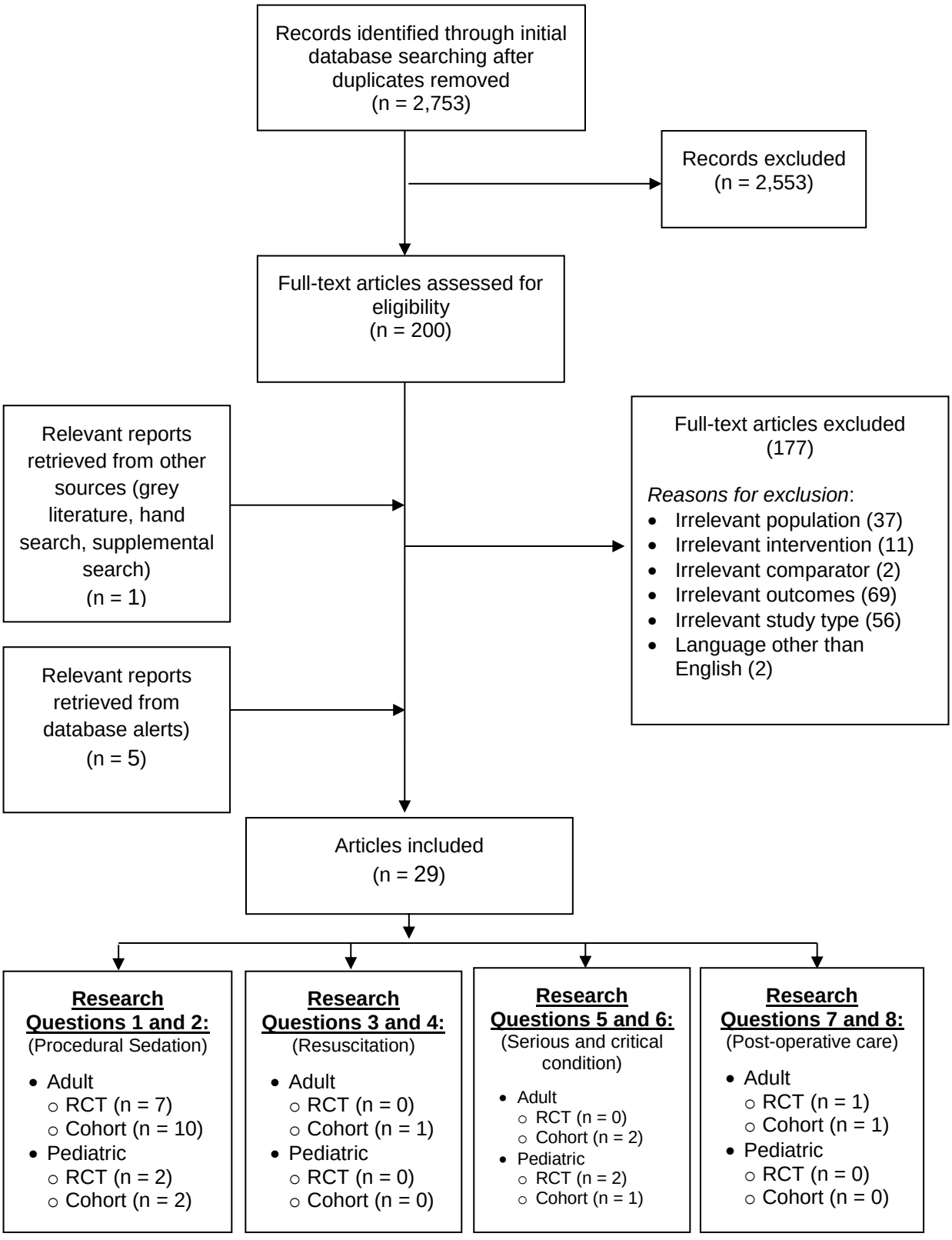
ASA = American Society of Anesthesiologists; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; HR = hazard ratio; RCT = randomized controlled trial; RR = risk ratio.

[a] Continuous outcomes.

[b] Research Questions 1 and 2: detection of respiratory failure (hypoxemia or hypercapnia), detection of a respiratory event (i.e., hypoventilation, hyperventilation, apnea, airway obstruction), time to detection of a respiratory event, change in clinical management (i.e., re-evaluate patients, avoid use of more sedative). Research Questions 3 and 4: survival of acute event, return of spontaneous circulation, effectiveness of chest compressions, detection of respiratory failure (hypoxemia, hypercapnia), change in clinical management (i.e., continue or withhold chest compressions, re-evaluate patients). Research Questions 5 to 8: detection of respiratory failure (hypoxemia or hypercapnia), detection of a respiratory event (i.e., hypoventilation, hyperventilation, apnea, airway obstruction), time to detection of a respiratory event, change in clinical management (i.e., re-evaluate patients, provide airway support). All clinical Research Questions (1 to 8): survival to hospital discharge, discharge with full neurological functioning, hypoxemia, organ damage, ventilation variables, hemodynamic variables, length of stay in hospital, correct placement of endotracheal tube, displacement of ventilation or intubation tube, adverse events related to the capnography device (i.e., misinterpretation of capnography readings, capnography device malfunction).

[c] Binary or time to event outcomes.

APPENDIX 5: Study Selection Flow Diagram — Clinical Review



APPENDIX 6: List of Studies Excluded From the Clinical Review and Reasons For Exclusion

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Abdelmalak B, Wang J, Mehta A. Capnography monitoring in procedural sedation for bronchoscopy. J Bronchology Interv Pulmonol. 2014 Jul;21(3):188-91.	Study type
Abraham A, Peled N, Khlebtovsky A, Benninger F, Steiner I, Stiebel-Kalish H, et al. Nocturnal carbon dioxide monitoring in patients with idiopathic intracranial hypertension. Clin Neurol Neurosurg. 2013 Aug;115(8):1379-81.	Population
Adams L, Butas S, Spurlock D, Jr. Capnography ($ETCO_2$), respiratory depression, and nursing interventions in moderately sedated adults undergoing transesophageal echocardiography (TEE). J Perianesth Nurs. 2015 Feb;30(1):14-22.	Outcomes
Adi O, Chuan TW, Rishya M. A feasibility study on bedside upper airway ultrasonography compared to waveform capnography for verifying endotracheal tube location after intubation. Crit ultrasound J. 2013;5(1):7.	Outcomes
Agus MS, Alexander JL, Mantell PA. Continuous non-invasive end-tidal CO_2 monitoring in pediatric inpatients with diabetic ketoacidosis. Pediatr Diabetes. 2006 Aug;7(4):196-200.	Outcomes
Aichinger G, Zechner PM, Prause G, Sacherer F, Wildner G, Anderson CL, et al. Cardiac movement identified on prehospital echocardiography predicts outcome in cardiac arrest patients. Prehosp Emerg Care. 2012 Apr;16(2):251-5.	Study type
Akavipat P, Ittichaikulthol W, Tuchinda L, Sothikarnmanee T, Klanarong S, Pranootnarabhal T. The Thai anesthesia incidents (THAI Study) of anesthetic risk factors related to perioperative death and perioperative cardiovascular complications in intracranial surgery. J Med Assoc Thai. 2007 Aug;90(8):1565-72.	Population
Akinci E, Ramadan H, Yuzbasioglu Y, Coskun F. Comparison of end-tidal carbon dioxide levels with cardiopulmonary resuscitation success presented to emergency department with cardiopulmonary arrest. Pakistan Journal of Medical Sciences. 2013;30(1).	Study type
Albrecht E, Yersin B, Spahn DR, Fishman D, Hugli O. Success rate of airway management by residents in a pre-hospital emergency setting: A retrospective study. European Journal of Trauma. 2006;32(6):516-22.	Study type
Arakawa H, Kaise M, Sumiyama K, Saito S, Suzuki T, Tajiri H. Does pulse oximetry accurately monitor a patient's ventilation during sedated endoscopy under oxygen supplementation? Singapore Med J. 2013 Apr;54(4):212-5.	Intervention
Axelsson C, Karlsson T, Axelsson AB, Herlitz J. Mechanical active compression-decompression cardiopulmonary resuscitation (ACD-CPR) versus manual CPR according to pressure of end tidal carbon dioxide ($P(ET)CO_2$) during CPR in out-of-hospital cardiac arrest (OHCA). Resuscitation. 2009 Oct;80(10):1099-103.	Study type
Belpomme V, Ricard-Hibon A, Devoir C, Dileseigres S, Devaud ML, Chollet C, et al. Correlation of arterial PCO_2 and $PETCO_2$ in prehospital controlled ventilation. Am J Emerg Med. 2005 Nov;23(7):852-9.	Outcomes
Berkenstadt H, Ben-Menachem E, Herman A, Dach R. An evaluation of the Integrated Pulmonary Index (IPI) for the detection of respiratory events in sedated patients undergoing colonoscopy. J Clin Monit Comput. 2012 Jun;26(3):177-81.	Outcomes
Bhananker SM, Posner KL, Cheney FW, Caplan RA, Lee LA, Domino KB. Injury and liability associated with monitored anesthesia care: a closed claims analysis. Anesthesiology. 2006 Feb;104(2):228-34.	Study type
Bradley B, Green GC, Batkin I, Seely AJ. Feasibility of continuous multiorgan variability analysis in the intensive care unit. J Crit Care. 2012 Apr;27(2):218-20.	Study type

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Brandt PA. Assess your adequacy. Use capnography & automated CPR devices to measure your effectiveness. J Emerg Med Serv JEMS. 2009 Sep;Suppl:suppl 14-7, 2009 Sep.:-7.	study type
Brazinova A, Majdan M, Leitgeb J, Trimmel H, Mauritz W, Austrian Working Group on Improvement of Early TBI Care. Factors that may improve outcomes of early traumatic brain injury care: prospective multicenter study in Austria. Scand J Trauma Resusc Emerg Med. 2015;23(1):53.	Intervention
Brun PM, Bessereau J, Cazes N, Querellou E, Chenaitia H. Lung ultrasound associated to capnography to verify correct endotracheal tube positioning in prehospital. Am J Emerg Med. 2012 Nov;30(9):2080-6.	Study type
Burns SM, Carpenter R, Blevins C, Bragg S, Marshall M, Browne L, et al. Detection of inadvertent airway intubation during gastric tube insertion: Capnography versus a colorimetric carbon dioxide detector. Am J Crit Care. 2006 Mar;15(2):188-95.	Population
Caulfield EV, Dutton RP, Floccare DJ, Stansbury LG, Scalea TM. Prehospital hypocapnia and poor outcome after severe traumatic brain injury. J Trauma. 2009 Jun;66(6):1577-82.	Study type
Charuluxananan S, Punjasawadwong Y, Suraseranivongse S, Srisawasdi S, Kyokong O, Chinachoti T, et al. The Thai Anesthesia Incidents Study (THAI Study) of anesthetic outcomes : II anesthetic profiles and adverse events. J Med Assoc Thai. 2005;88(Suppl 7):S14-S29.	Study type
Charuluxananan S, Suraseranivongse S, Jantorn P, Sriraj W, Chanchayanon T, Tanudsintum S, et al. Multicentered study of model of anesthesia related adverse events in Thailand by incident report (the Thai anesthesia incidents monitoring study): Results. J Med Assoc Thai. 2008;91(7):1011-9.	Intervention
Chen F, Chin K, Ishii H, Kubo H, Miwa S, Ikeda T, et al. Continuous carbon dioxide partial pressure monitoring in lung transplant recipients. Ann Transplant. 2014;19:382-8.	Outcomes
Chhajed PN, Miedinger D, Baty F, Bernasconi M, Heuss LT, Leuppi JD, et al. Comparison of combined oximetry and cutaneous capnography using a digital sensor with arterial blood gas analysis. Scand J Clin Lab Invest. 2010 Feb;70(1):60-4.	Intervention
Chou HC, Chong KM, Sim SS, Ma MH, Liu SH, Chen NC, et al. Real-time tracheal ultrasonography for confirmation of endotracheal tube placement during cardiopulmonary resuscitation. Resuscitation. 2013 Dec;84(12):1708-12.	Outcomes
Chou HC, Tseng WP, Wang CH, Ma MH, Wang HP, Huang PC, et al. Tracheal rapid ultrasound exam (T.R.U.E.) for confirming endotracheal tube placement during emergency intubation. Resuscitation. 2011 Oct;82(10):1279-84.	Outcomes
Cinar O, Acar YA, Arziman I, Kilic E, Eyi YE, Ocal R. Can mainstream end-tidal carbon dioxide measurement accurately predict the arterial carbon dioxide level of patients with acute dyspnea in ED. Am J Emerg Med. 2012 Feb;30(2):358-61.	Outcomes
Coates BM, Chaize R, Goodman DM, Rozenfeld RA. Performance of capnometry in non-intubated infants in the pediatric intensive care unit. BMC Pediatr. 2014;14:163.	Outcomes
Connor L, Zurakowski D, Stazinski A, Bucci K, MacPherson S, Perich M, et al. Monitoring end-tidal carbon dioxide levels of deeply sedated MRI pediatric patients during the recovery period. J Radiol Nurs. 2009;28(2):51-5.	Study type
Contal O, Adler D, Borel JC, Espa F, Perrig S, Rodenstein D, et al. Impact of different backup respiratory rates on the efficacy of noninvasive positive pressure ventilation in obesity hypoventilation syndrome: a randomized trial. Chest. 2013 Jan;143(1):37-46.	Intervention
Cook T, Harper J, Woodall N. Report of the NAP4 airway project. Journal of the Intensive Care Society. 2011;12(2):107-11.	Population

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth. 2011 May;106(5):632-42.	Study type
Coté CJ, Wax DF, Jennings MA, Gorski CL, Kurczak-Klippstein K. Endtidal carbon dioxide monitoring in children with congenital heart disease during sedation for cardiac catheterization by nonanesthesiologists. Paediatr Anaesth. 2007;17(7):661-6.	Outcomes
Davis DP, Aguilar S, Sonnleitner C, Cohen M, Jennings M. Latency and loss of pulse oximetry signal with the use of digital probes during prehospital rapid-sequence intubation. Prehosp Emerg Care. 2011 Jan;15(1):18-22.	Study type
Davis DP, Douglas DJ, Koenig W, Carrison D, Buono C, Dunford JV. Hyperventilation following aero-medical rapid sequence intubation may be a deliberate response to hypoxemia. Resuscitation. 2007;73(3):354-61.	Outcomes
Davis DP, Fisher R, Buono C, Brainard C, Smith S, Ochs G, et al. Predictors of intubation success and therapeutic value of paramedic airway management in a large, urban EMS system. Prehosp Emerg Care. 2006;10(3):356-62.	Study type
Davis DP, Sell RE, Wilkes N, Sarno R, Husa RD, Castillo EM, et al. Electrical and mechanical recovery of cardiac function following out-of-hospital cardiac arrest. Resuscitation. 2013;84(1):25-30.	Study type
Delerme S, Freund Y, Renault R, Devilliers C, Castro S, Chopin S, et al. Concordance between capnography and capnia in adults admitted for acute dyspnea in an ED. Am J Emerg Med. 2010 Jul;28(6):711-4.	Outcomes
Della Via F, Oliveira RA, Dragosavac D. Effects of manual chest compression and descompression maneuver on lung volumes, capnography and pulse oximetry in patients receiving mechanical ventilation. Rev Bras Fisioter. 2012 Sep;16(5):354-9.	Study type
Dion JM, McKee C, Tobias JD, Herz D, Sohner P, Teich S, et al. Carbon dioxide monitoring during laparoscopic-assisted bariatric surgery in severely obese patients: transcutaneous versus end-tidal techniques. J Clin Monit Comput. 2015 Feb;29(1):183-6.	Outcomes
Dogan NO, Sener A, Gunaydin GP, Icme F, Celik GK, Kavakli HS, et al. The accuracy of mainstream end-tidal carbon dioxide levels to predict the severity of chronic obstructive pulmonary disease exacerbations presented to the ED. Am J Emerg Med. 2014 May;32(5):408-11.	Study type
Donnelly N, Hunniford T, Harper R, Flynn A, Kennedy A, Branagh D, et al. Demonstrating the accuracy of an in-hospital ambulatory patient monitoring solution in measuring respiratory rate. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:6711-5, 2013.:-5.	Population
Dunham CM, Chirichella TJ, Gruber BS, Ferrari JP, Martin JA, Luchs BA, et al. Emergency department noninvasive (NICOM) cardiac outputs are associated with trauma activation, patient injury severity and host conditions and mortality. J Trauma Acute Care Surg. 2012 Aug;73(2):479-85.	Outcomes
Dunham CM, Chirichella TJ, Gruber BS, Ferrari JP, Martin JA, Luchs BA, et al. In emergently ventilated trauma patients, low end-tidal CO_2 and low cardiac output are associated and correlate with hemodynamic instability, hemorrhage, abnormal pupils, and death. BMC Anesthesiology. 2013;13.	Study type
Dyer BA, White WA, Jr., Lee D, Elkins L, Slayton DJ. The relationship between arterial carbon dioxide tension and end-tidal carbon dioxide tension in intubated adults with traumatic brain injuries who required emergency craniotomies. Crit Care Nurs Q. 2013 Jul;36(3):310-5.	Study type
Dziewas R, Hopmann B, Humpert M, Bontert M, Dittrich R, Ludemann P, et al. Capnography screening for sleep apnea in patients with acute stroke. Neurol Res. 2005 Jan;27(1):83-7.	Population

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Ebert TJ, Novalija J, Uhrich TD, Barney JA. The effectiveness of oxygen delivery and reliability of carbon dioxide waveforms: A crossover comparison of 4 Nasal cannulae. Anesth Analg. 2015;120(2):342-8.	Population
Edelson DP, Eilevstjonn J, Weidman EK, Retzer E, Hoek TL, Abella BS. Capnography and chest-wall impedance algorithms for ventilation detection during cardiopulmonary resuscitation. Resuscitation. 2010 Mar;81(3):317-22.	Outcomes
Einav S, Bromiker R, Weiniger CF, Matot I. Mathematical modeling for prediction of survival from resuscitation based on computerized continuous capnography: proof of concept. Acad Emerg Med. 2011 May;18(5):468-75.	Study type
Ellett ML, Woodruff KA, Stewart DL. The use of carbon dioxide monitoring to determine orogastric tube placement in premature infants: a pilot study. Gastroenterol Nurs. 2007 Nov;30(6):414-7.	Population
Elpern EH, Killeen K, Talla E, Perez G, Gurka D. Capnometry and air insufflation for assessing initial placement of gastric tubes. Am J Crit Care. 2007 Nov;16(6):544-9.	Population
Fouzas S, Hacki C, Latzin P, Proietti E, Schulzke S, Frey U, et al. Volumetric capnography in infants with bronchopulmonary dysplasia. J Pediatr. 2014 Feb;164(2):283-8.	Population
Fuchs J, Schummer C, Giesser J, Bayer O, Schummer W. Detection of tracheal malpositioning of nasogastric tubes using endotracheal cuff pressure measurement. Acta Anaesthesiol Scand. 2007 Oct;51(9):1245-9.	Population
Galia F, Brimioulle S, Bonnier F, Vandenbergen N, Dojat M, Vincent JL, et al. Use of maximum end-tidal CO_2 values to improve end-tidal CO_2 monitoring accuracy. Respir Care. 2011 Mar;56(3):278-83.	Outcomes
Gaucher A, Frasca D, Mimoz O, Debaene B. Accuracy of respiratory rate monitoring by capnometry using the Capnomask® in extubated patients receiving supplemental oxygen after surgery. Br J Anaesth. 2012 Feb;108(2):316-20.	Outcomes
Georgiou AP, Gouldson S, Amphlett AM. Erratum: The use of capnography and the availability of airway equipment on Intensive Care Units in the UK and Republic of Ireland (Anaesthesia (2010) 65 (462-467)). Anaesthesia. 2010;65(6):658.	Study type
Goonasekera CD, Goodwin A, Wang Y, Goodman J, Deep A. Arterial and end-tidal carbon dioxide difference in pediatric intensive care. Ind J Crit Care Med. 2014 Nov;18(11):711-5.	Population
Gowda H. Question 2. Should carbon dioxide detectors be used to check correct placement of endotracheal tubes in preterm and term neonates? Arch Dis Child. 2011 Dec;96(12):1201-3.	Study type
Green GC, Bradley B, Bravi A, Seely AJ. Continuous multiorgan variability analysis to track severity of organ failure in critically ill patients. J Crit Care. 2013 Oct;28(5):879-11.	Outcomes
Grmec Š, Križmaric M, Mally Š, Koželj A, Špindler M, Lešnik B. Utstein style analysis of out-of-hospital cardiac arrest-Bystander CPR and end expired carbon dioxide. Resuscitation. 2007;72(3):404-14.	Study type
Guechi Y, Pichot A, Frasca D, Rayeh-Pelardy F, Lardeur JY, Mimoz O. Assessment of noninvasive acoustic respiration rate monitoring in patients admitted to an Emergency Department for drug or alcoholic poisoning. J Clin Monit Comput. 2015 Dec;29(6):721-6.	Outcomes
Guirgis FW, Williams DJ, Kalynych CJ, Hardy ME, Jones AE, Dodani S, et al. End-tidal carbon dioxide as a goal of early sepsis therapy. Am J Emerg Med. 2014 Nov;32(11):1351-6.	Study type
Hamrick JL, Hamrick JT, Lee JK, Lee BH, Koehler RC, Shaffner DH. Efficacy of chest compressions directed by end-tidal CO_2 feedback in a pediatric resuscitation model of basic life support. J Am Heart Assoc. 2014;3(2):e000450.	Population

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Hartdorff CM, van HM, Markhorst DG. Bench test assessment of mainstream capnography during high frequency oscillatory ventilation. J Clin Monit Comput. 2014 Feb;28(1):63-6.	Population
Hawkes GA, Kenosi M, Ryan CA, Dempsey EM. Quantitative or qualitative carbon dioxide monitoring for manual ventilation: a mannequin study. Acta Paediatr. 2015 Apr;104(4):e148-e151.	Population
Heines SJ, Strauch U, Roekaerts PM, Winkens B, Bergmans DC. Accuracy of end-tidal CO_2 capnometers in post-cardiac surgery patients during controlled mechanical ventilation. J Emerg Med. 2013 Jul;45(1):130-5.	Outcomes
Heradstveit BE, Sunde K, Sunde GA, Wentzel-Larsen T, Heltne JK. Factors complicating interpretation of capnography during advanced life support in cardiac arrest--a clinical retrospective study in 575 patients. Resuscitation. 2012 Jul;83(7):813-8.	Study type
Heuss LT, Sugandha SP, Beglinger C. Carbon dioxide accumulation during analgosedated colonoscopy: comparison of propofol and midazolam. World J Gastroenterol. 2012 Oct 14;18(38):5389-96.	Study type
Hildebrandt T, Espelund M, Olsen KS. Evaluation of a transportable capnometer for monitoring end-tidal carbon dioxide. Anaesthesia. 2010 Oct;65(10):1017-21.	Outcomes
Hiller J, Silvers A, McIlroy DR, Niggemeyer L, White S. A retrospective observational study examining the admission arterial to end-tidal carbon dioxide gradient in intubated major trauma patients. Anaesth Intensive Care. 2010 Mar;38(2):302-6.	Outcomes
Hinkelbein J, Floss F, Denz C, Krieter H. Accuracy and precision of three different methods to determine Pco2 (Paco2 vs. Petco2 vs. Ptcco2) during interhospital ground transport of critically ill and ventilated adults. J Trauma. 2008 Jul;65(1):10-8.	Outcomes
Hodges E, Griffiths A, Richardson J, Blunt M, Young P. Emergency capnography monitoring: comparing ergonomic design of intensive care unit ventilator interfaces and specific training of staff in reducing time to activation. Anaesthesia. 2012 Aug;67(8):850-4.	Population
Hosono S, Inami I, Fujita H, Minato M, Takahashi S, Mugishima H. A role of end-tidal CO(2) monitoring for assessment of tracheal intubations in very low birth weight infants during neonatal resuscitation at birth. J Perinat Med. 2009;37(1):79-84.	Outcomes
Howe TA, Jaalam K, Ahmad R, Sheng CK, Nik Ab Rahman NH. The use of end-tidal capnography to monitor non-intubated patients presenting with acute exacerbation of asthma in the emergency department. J Emerg Med. 2011 Dec;41(6):581-9.	Outcomes
Howes DW, Shelley ES, Pickett W. Colorimetric carbon dioxide detector to determine accidental tracheal feeding tube placement. Can J Anaesth. 2005 Apr;52(4):428-32.	Population
Hwang WS, Park JS, Kim SJ, Hong YS, Moon SW, Lee SW. A system-wide approach from the community to the hospital for improving neurologic outcomes in out-of-hospital cardiac arrest patients. Eur J Emerg Med. 2015 Aug 11.	Intervention
Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med. 2010 Feb;36(2):248-55.	Intervention
Jabre P, Jacob L, Auger H, Jaulin C, Monribot M, Aurore A, et al. Capnography monitoring in nonintubated patients with respiratory distress. Am J Emerg Med. 2009 Nov;27(9):1056-9.	Outcomes
Jacob R, Nelkenbaum A, Merrick J, Brik R. Capnography in patients with severe neurological impairment. Res Dev Disabil. 2014 Jun;35(6):1259-63.	Population

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Jaimchariyatam N, Dweik RA, Kaw R, Aboussouan LS. Polysomnographic determinants of nocturnal hypercapnia in patients with sleep apnea. J Clin Sleep Med. 2013 Mar 15;9(3):209-15.	Population
Johnson DC, Batool S, Dalbec R. Transcutaneous carbon dioxide pressure monitoring in a specialized weaning unit. Respir Care. 2008 Aug;53(8):1042-7.	Outcomes
Kang LJ, Cheung PY, Pichler G, O'Reilly M, Aziz K, Schmolzer GM. Monitoring lung aeration during respiratory support in preterm infants at birth. PLoS One. 2014;9(7):e102729.	Study type
Kartal M, Eray O, Rinnert S, Goksu E, Bektas F, Eken C. $ETCO_2$: a predictive tool for excluding metabolic disturbances in nonintubated patients. Am J Emerg Med. 2011 Jan;29(1):65-9.	Outcomes
Kartal M, Goksu E, Eray O, Isik S, Sayrac AV, Yigit OE, et al. The value of $ETCO_2$ measurement for COPD patients in the emergency department. Eur J Emerg Med. 2011 Feb;18(1):9-12.	Outcomes
Kasuya Y, Akca O, Sessler DI, Ozaki M, Komatsu R. Accuracy of postoperative end-tidal Pco2 measurements with mainstream and sidestream capnography in non-obese patients and in obese patients with and without obstructive sleep apnea. Anesthesiology. 2009 Sep;111(3):609-15.	Outcomes
Kheng CP, Rahman NH. The use of end-tidal carbon dioxide monitoring in patients with hypotension in the emergency department. Int J Emerg Med. 2012;5(1).	Study type
Kim HY, Kim GS, Shin YH, Cha SR. The usefulness of end-tidal carbon dioxide monitoring during apnea test in brain-dead patients. Korean Journal Anesthesiol. 2014 Sep;67(3):186-92.	Outcomes
Kim JY, Min HG, Ha SI, Jeong HW, Seo H, Kim JU. Dynamic optic nerve sheath diameter responses to short-term hyperventilation measured with sonography in patients under general anesthesia. Korean Journal Anesthesiol. 2014 Oct;67(4):240-5.	Population
Kim KW, Choi HR, Bang SR, Lee JW. Comparison of end-tidal CO measured by transportable capnometer (EMMA capnograph) and arterial pCO in general anesthesia. J Clin Monit Comput. 2015 Aug 12.	Population
Kingston EV, Loh NH. Use of capnography may cause airway complications in intensive care. Br J Anaesth. 2014 Feb;112(2):388-9.	Study type
Kirk VG, Batuyong ED, Bohn SG. Transcutaneous carbon dioxide monitoring and capnography during pediatric polysomnography. Sleep. 2006 Dec;29(12):1601-8.	Population
Kjorven M, Dunton D, Milo R, Gerein L. Bedside capnography: better management of surgical patients with obstructive sleep apnea. Can Nurse. 2011 Nov;107(9):24-6.	Study type
Klimek J, Morley CJ, Lau R, Davis PG. Does measuring respiratory function improve neonatal ventilation? J Paediatr Child Health. 2006 Mar;42(3):140-2.	Intervention
Kodali BS. Capnometry versus acoustic device for monitoring respiration. Anesth Analg. 2014;118(2):485-6.	Study type
Krauss B, Hess DR. Capnography for procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2007 Aug;50(2):172-81.	Study type
Kugelman A, Riskin A, Shoris I, Ronen M, Stein IS, Bader D. Continuous integrated distal capnography in infants ventilated with high frequency ventilation. Pediatr Pulmonol. 2012 Sep;47(9):876-83.	Study type
Kugelman A, Zeiger-Aginsky D, Bader D, Shoris I, Riskin A. A novel method of distal end-tidal CO_2 capnography in intubated infants: comparison with arterial CO_2 and with proximal mainstream end-tidal CO_2. Pediatrics. 2008 Dec;122(6):e1219-e1224.	Outcomes

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Kunkov S, Pinedo V, Silver EJ, Crain EF. Predicting the need for hospitalization in acute childhood asthma using end-tidal capnography. Pediatr Emerg Care. 2005 Sep;21(9):574-7.	Study type
Kusumaphanyo C, Charuluxananan S, Sriramatr D, Pulnitiporn A, Sriraj W. The Thai Anesthesia Incident Monitoring Study (Thai AIMS) of anesthetic equipment failure/malfunction: an analysis of 1996 incident reports. J Med Assoc Thai. 2009 Nov;92(11):1442-9.	Population
Kusunoki R, Amano Y, Yuki T, Oka A, Okada M, Tada Y, et al. Erratum: Capnographic monitoring for carbon dioxide insufflation during endoscopic submucosal dissection: Comparison of transcutaneous and end-tidal capnometers. Surgical Endoscopy and Other Interventional Techniques. 2012;26(2):507.	Study type
Langhan ML. Acute alcohol intoxication in adolescents: frequency of respiratory depression. J Emerg Med. 2013 Jun;44(6):1063-9.	Comparator
Langhan ML, Auerbach M, Smith AN, Chen L. Improving detection by pediatric residents of endotracheal tube dislodgement with capnography: a randomized controlled trial. J Pediatr. 2012 Jun;160(6):1009-14.	Population
Langhan ML, Chen L, Marshall C, Santucci KA. Detection of hypoventilation by capnography and its association with hypoxia in children undergoing sedation with ketamine. Pediatr Emerg Care. 2011 May;27(5):394-7.	Population
Langhan ML, Ching K, Northrup V, Alletag M, Kadia P, Santucci K, et al. A randomized controlled trial of capnography in the correction of simulated endotracheal tube dislodgement. Acad Emerg Med. 2011 Jun;18(6):590-6.	Outcomes
Law GTS, Wong CY, Kwan CW, Wong KY, Wong FP, Tse HN. Concordance between side-stream end-tidal carbon dioxide and arterial carbon dioxide partial pressure in respiratory service setting. Hong Kong Med J. 2009;15(6):440-6.	Outcomes
Lindstrom V, Svensen CH, Meissl P, Tureson B, Castrén M. End-tidal carbon dioxide monitoring during bag valve ventilation: the use of a new portable device. Scand J Trauma Resusc Emerg Med. 2010;18:49.	Population
Lopez E, Grabar S, Barbier A, Krauss B, Jarreau PH, Moriette G. Detection of carbon dioxide thresholds using low-flow sidestream capnography in ventilated preterm infants. Intensive Care Med. 2009 Nov;35(11):1942-9.	Outcomes
López-Herce J, Mencia S, Santiago MJ, Herrera M, Solana MJ. Hypoventilation due to reinhalation in infants with a transport ventilator. Pediatr Emerg Care. 2009 Sep;25(9):588-9.	Study type
Lujan M, Canturri E, Moreno A, Arranz M, Vigil L, Domingo C. Capnometry in spontaneously breathing patients: the influence of chronic obstructive pulmonary disease and expiration maneuvers. Med Sci Monit. 2008 Sep;14(9):CR485-CR492.	Outcomes
Marciniak B, Fayoux P, Hebrard A, Krivosic-Horber R, Engelhardt T, Bissonnette B. Airway management in children: ultrasonography assessment of tracheal intubation in real time? Anesth Analg. 2009 Feb;108(2):461-5.	Population
Martinon C, Duracher C, Blanot S, Escolano S, De AM, Perie-Vintras AC, et al. Emergency tracheal intubation of severely head-injured children: changing daily practice after implementation of national guidelines. Pediatr Crit Care Med. 2011 Jan;12(1):65-70.	Study type
McCarter T, Shaik Z, Scarfo K, Thompson LJ. Capnography monitoring enhances safety of postoperative patient-controlled analgesia. Am Health Drug Benefits. 2008 Jun;1(5):28-35.	Outcomes
Mensour M, Pineau R, Sahai V, Michaud J. Emergency department procedural sedation and analgesia: A Canadian Community Effectiveness and Safety Study (ACCESS). Canadian Journal of Emergency Medicine. 2006;8(2):94-9.	Intervention

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Miller KM, Kim AY, Yaster M, Kudchadkar SR, White E, Fackler J, et al. Long-term tolerability of capnography and respiratory inductance plethysmography for respiratory monitoring in pediatric patients treated with patient-controlled analgesia. Paediatr Anaesth. 2015 Jun 3.	Outcomes
Miner JR, Gray RO, Stephens D, Biros MH. Randomized clinical trial of propofol with and without alfentanil for deep procedural sedation in the emergency department. Acad Emerg Med. 2009;16(9):825-34.	Outcomes
Monaco F, Drummond GB, Ramsay P, Servillo G, Walsh TS. Do simple ventilation and gas exchange measurements predict early successful weaning from respiratory support in unselected general intensive care patients? Br J Anaesth. 2010;105(3):326-33.	Study type
Nagurka R, Bechmann S, Gluckman W, Scott SR, Compton S, Lamba S. Utility of initial prehospital end-tidal carbon dioxide measurements to predict poor outcomes in adult asthmatic patients. Prehosp Emerg Care. 2014 Apr;18(2):180-4.	Study type
Niesters M, Mahajan R, Olofsen E, Boom M, Garcia del Valle S, Aarts L, et al. Validation of a novel respiratory rate monitor based on exhaled humidity. Br J Anaesth. 2012;109(6):981-9.	Outcomes
Nik Ab Rahman NH, Mamat AF. The use of capnometry to predict arterial partial pressure of CO_2 in non-intubated breathless patients in the emergency department. Int J Emerg Med. 2010;3(4):315-20.	Outcomes
Overdyk FJ, Carter R, Maddox RR, Callura J, Herrin AE, Henriquez C. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. Anesth Analg. 2007 Aug;105(2):412-8.	Outcomes
Ozturk F, Parlak I, Yolcu S, Tomruk O, Erdur B, Kilicaslan R, et al. Effect of end-tidal carbon dioxide measurement on resuscitation efficiency and termination of resuscitation. Turkiye Acil Tip Dergisi. 2014;14(1):25-31.	Study type
Ozyuvaci E, Demircioglu O, Toprak N, Topacoglu H, Sitilci T, Akyol O. Comparison of transcutaneous, arterial and end-tidal measurements of carbon dioxide during laparoscopic cholecystectomy in patients with chronic obstructive pulmonary disease. J Int Med Res. 2012;40(5):1982-7.	Outcomes
Pandia MP, Bithal PK, Dash HH, Chaturvedi A. Comparative incidence of cardiovascular changes during venous air embolism as detected by transesophageal echocardiography alone or in combination with end tidal carbon dioxide tension monitoring. J Clin Neurosci. 2011;18(9):1206-9.	Population
Patino M, Redford DT, Quigley TW, Mahmoud M, Kurth CD, Szmuk P. Accuracy of acoustic respiration rate monitoring in pediatric patients. Paediatr Anaesth. 2013 Dec;23(12):1166-73.	Outcomes
Pearce AK, Davis DP, Minokadeh A, Sell RE. Initial end-tidal carbon dioxide as a prognostic indicator for inpatient PEA arrest. Resuscitation. 2015 Jul;92:77-81, 2015 Jul.:-81.	Study type
Pekdemir M, Cinar O, Yilmaz S, Yaka E, Yuksel M. Disparity between mainstream and sidestream end-tidal carbon dioxide values and arterial carbon dioxide levels. Respir Care. 2013 Jul;58(7):1152-6.	Outcomes
Pfeiffer P, Bache S, Isbye DL, Rudolph SS, Rovsing L, Borglum J. Verification of endotracheal intubation in obese patients - temporal comparison of ultrasound vs. auscultation and capnography. Acta Anaesthesiol Scand. 2012 May;56(5):571-6.	Population
Pfeiffer P, Rudolph SS, Borglum J, Isbye DL. Temporal comparison of ultrasound vs. auscultation and capnography in verification of endotracheal tube placement. Acta Anaesthesiol Scand. 2011 Nov;55(10):1190-5.	Outcomes
Phelan MP, Ornato JP, Peberdy MA, Hustey FM, American Heart Association's Get With The Guidelines-Resuscitation Investigators. Appropriate documentation of confirmation of endotracheal tube position and relationship to patient outcome from in-hospital cardiac arrest. Resuscitation. 2013 Jan;84(1):31-6.	Intervention

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Poeze M, Solberg BC, Greve JW, Ramsay G. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: What is a better predictor of outcome in critically ill septic patients? Crit Care Med. 2005 Nov;33(11):2494-500.	Outcomes
Prathanvanich P, Chand B. The role of capnography during upper endoscopy in morbidly obese patients: a prospective study. Surg. 2015 Jan;obes. relat. dis.. 11(1):193-8.	Comparator
Price DD, Wilson SR, Fee ME. Sidestream end-tidal carbon dioxide monitoring during helicopter transport. Air Medical Journal. 2007;26(1):55-9.	Study type
Qvigstad E, Kramer-Johansen J, Tomte O, Skalhegg T, Sorensen O, Sunde K, et al. Clinical pilot study of different hand positions during manual chest compressions monitored with capnography. Resuscitation. 2013 Sep;84(9):1203-7.	Study type
Rasera CC, Gewehr PM, Domingues AM. PET(CO_2) measurement and feature extraction of capnogram signals for extubation outcomes from mechanical ventilation. Physiol Meas. 2015 Feb;36(2):231-42.	Outcomes
Rosier S, Launey Y, Bleichner JP, Laviolle B, Jouve A, Malledant Y, et al. The accuracy of transcutaneous PCO2 in subjects with severe brain injury: A comparison with End-Tidal PCO2. Respir Care. 2014;59(8):1242-7.	Outcomes
Rowan CM, Speicher RH, Hedlund T, Ahmed SS, Swigonski NL. Implementation of continuous capnography is associated with a decreased utilization of blood gases. J Clin Med Res. 2015 Feb;7(2):71-5.	Outcomes
Sakata DJ, Matsubara I, Gopalakrishnan NA, Westenskow DR, White JL, Yamamori S, et al. Flow-through versus sidestream capnometry for detection of end tidal carbon dioxide in the sedated patient. J Clin Monit Comput. 2009 Apr;23(2):115-22.	Population
Sanchez-Zurita H. [Outcome of patients monitored with pulse oximetry and capnography during anesthesia]. Revista Mexicana de Anestesiologia. 2011;34(Suppl 1):S21-S22. Spanish.	Language
Schmolzer GM, Poulton DA, Dawson JA, Kamlin CO, Morley CJ, Davis PG. Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation. Resuscitation. 2011 Mar;82(3):307-12.	Outcomes
Segal N, Parquette B, Ziehr J, Yannopoulos D, Lindstrom D. Intrathoracic pressure regulation during cardiopulmonary resuscitation: a feasibility case series. Resuscitation. 2013 Apr;84(4):450-3.	Study type
Sheak KR, Wiebe DJ, Leary M, Babaeizadeh S, Yuen TC, Zive D, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. Resuscitation. 2015 Apr;89:149-54, 2015 Apr.:-54.	Study type
Shetty AL, Lai KH, Byth K. The CO_2 GAP Project--CO_2 GAP as a prognostic tool in emergency departments. Emerg Med Australas. 2010 Dec;22(6):524-31.	Study type
Sierra G, Telfort V, Popov B, Pelletier M, Despault P, Agarwal R, et al. Comparison of respiratory rate estimation based on tracheal sounds versus a capnograph. Conf Proc IEEE Eng Med Biol Soc. 2005;6:6145-8, 2005.:-8.	Population
Singh BS, Gilbert U, Singh S, Govindaswami B. Sidestream microstream end tidal carbon dioxide measurements and blood gas correlations in neonatal intensive care unit. Pediatr Pulmonol. 2013 Mar;48(3):250-6.	Outcomes
Singh R, Neo EN, Nordeen N, Shanmuganathan G, Ashby A, Drummond S, et al. Carbon dioxide insufflation during colonoscopy in deeply sedated patients. World J Gastroenterol. 2012 Jul 7;18(25):3250-3.	Study type
Singh S, Allen WD, Jr., Venkataraman ST, Bhende MS. Utility of a novel quantitative handheld microstream capnometer during transport of critically ill children. Am J Emerg Med. 2006 May;24(3):302-7.	Study type

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Singh SA, Singhal N. Does end-tidal carbon dioxide measurement correlate with arterial carbon dioxide in extremely low birth weight infants in the first week of life? Indian Pediatr. 2006;43(1):20-5.	Outcomes
Sinha P, Fauvel NJ, Singh P, Soni N. Analysis of ventilatory ratio as a novel method to monitor ventilatory adequacy at the bedside. Crit Care. 2013;17(1):R34.	Outcomes
Sinha P, Soni N. Comparison of volumetric capnography and mixed expired gas methods to calculate physiological dead space in mechanically ventilated ICU patients. Intensive Care Med. 2012 Oct;38(10):1712-7.	Outcomes
Sivilotti ML, Messenger DW, van Vlymen J, Dungey PE, Murray HE. A comparative evaluation of capnometry versus pulse oximetry during procedural sedation and analgesia on room air. CJEM. 2010 Sep;12(5):397-404.	Outcomes
Smyrnios NA, Lenard R, Rajan S, Newman MS, Baker SP, Thakkar N, et al. Comparison of a self-inflating bulb syringe and a colorimetric CO_2 indicator with capnography and radiography to detect the misdirection of naso/orogastric tubes into the airway of critically ill adult patients. Chest. 2015 Jun;147(6):1523-9.	Population
Sun JT, Chou HC, Sim SS, Chong KM, Ma MHM, Wang HP, et al. Ultrasonography for proper endotracheal tube placement confirmation in out-of-hospital cardiac arrest patients: Two-center experience. J Med Ultrasound. 2014;22(2):83-7.	Outcomes
Szakal O, Kiraly A, Szucs D, Katona M, Boda D, Talosi G. Measurement of gastric-to-end-tidal carbon dioxide difference in neonates requiring intensive care. J Matern Fetal Neonatal Med. 2012 Sep;25(9):1791-5.	Study type
Takaki S, Mihara T, Mizutani K, Yamaguchi O, Goto T. Evaluation of an oxygen mask-based capnometry device in subjects extubated after abdominal surgery. Respir Care. 2015 May;60(5):705-10.	Outcomes
Takano A, Kobayashi M, Takeuchi M, Hashimoto S, Mizuno K, Narisawa R, et al. Capnographic monitoring during endoscopic submucosal dissection with patients under deep sedation: a prospective, crossover trial of air and carbon dioxide insufflations. Digestion. 2011;84(3):193-8.	Intervention
Terp S, Schriger DL. Routine capnographic monitoring is not indicated for all patients undergoing emergency department procedural sedation. Ann Emerg Med. 2013 Jun;61(6):698-9.	Study type
Thomas AN, McGrath BA. Patient safety incidents associated with airway devices in critical care: a review of reports to the UK National Patient Safety Agency. Anaesthesia. 2009 Apr;64(4):358-65.	Study type
Timmermann A, Russo SG, Eich C, Roessler M, Braun U, Rosenblatt WH, et al. The out-of-hospital esophageal and endobronchial intubations performed by emergency physicians. Anesth Analg. 2007 Mar;104(3):619-23.	Comparator
Tingay DG, Mun KS, Perkins EJ. End tidal carbon dioxide is as reliable as transcutaneous monitoring in ventilated postsurgical neonates. Arch Dis Child Fetal Neonatal Ed. 2013 Mar;98(2):F161-F164.	Outcomes
Tingay DG, Stewart MJ, Morley CJ. Monitoring of end tidal carbon dioxide and transcutaneous carbon dioxide during neonatal transport. Arch Dis Child Fetal Neonatal Ed. 2005 Nov;90(6):F523-F526.	Outcomes
Trevisanuto D, Giuliotto S, Cavallin F, Doglioni N, Toniazzo S, Zanardo V. End-tidal carbon dioxide monitoring in very low birth weight infants: correlation and agreement with arterial carbon dioxide. Pediatr Pulmonol. 2012 Apr;47(4):367-72.	Outcomes
Tusman G, Groisman I, Fiolo FE, Scandurra A, Arca JM, Krumrick G, et al. Noninvasive monitoring of lung recruitment maneuvers in morbidly obese patients: the role of pulse oximetry and volumetric capnography. Anesth Analg. 2014 Jan;118(1):137-44.	Population

Table 17: List of Excluded Studies From The Clinical Review

Study	Reason for Exclusion
Tusman G, Suarez-Sipmann F, Paez G, Alvarez J, Bohm SH. States of low pulmonary blood flow can be detected non-invasively at the bedside measuring alveolar dead space. J Clin Monit Comput. 2012 Jun;26(3):183-90.	Study type
van Vonderen JJ, Lista G, Cavigioli F, Hooper SB, Te Pas AB. Effectivity of ventilation by measuring expired CO_2 and RIP during stabilisation of preterm infants at birth. Arch Dis Child Fetal Neonatal Ed [Internet]. 2015 Jul 17.	Outcomes
Álvarez-Díaz N, Amador-García I, Fuentes-Hernández M, Dorta-Guerra R. Comparison between transthoracic lung ultrasound and a clinical method in confirming the position of double-lumen tube in thoracic anaesthesia. A pilot study. Rev Esp Anestesiol Reanim. 2015 Jun;62(6):305-12.	Language
Verschuren F, Heinonen E, Clause D, Zech F, Reynaert MS, Liistro G. Volumetric capnography: reliability and reproducibility in spontaneously breathing patients. Clin Physiol Funct Imaging. 2005 Sep;25(5):275-80.	Outcomes
Visnjevac O, Pourafkari L, Nader ND. Role of perioperative monitoring in diagnosis of massive intraoperative cardiopulmonary embolism. J Cardiovas Thorac Res. 2014;6(3):141-5.	Study type
Vivien B, Amour J, Nicolas-Robin A, Vesque M, Langeron O, Coriat P, et al. An evaluation of capnography monitoring during the apnoea test in brain-dead patients. Eur J Anaesthesiol. 2007 Oct;24(10):868-75.	Population
Wilbers NE, Hamaekers AE, Jansen J, Wijering SC, Thomas O, Wilbers-van RR, et al. Prehospital airway management: A prospective case study. Acta Anaesthesiol Belg. 2011;62(1):23-31.	Outcomes
Wilson J, Russo P, Russo J, Tobias JD. Noninvasive monitoring of carbon dioxide in infants and children with congenital heart disease: end-tidal versus transcutaneous techniques. J Intensive Care Med. 2005 Sep;20(5):291-5.	Outcomes
Winter MW. Intrahospital transfer of critically ill patients; a prospective audit within Flinders Medical Centre. Anaesth Intensive Care. 2010 May;38(3):545-9.	Study type
Won YH, Choi WA, Lee JW, Bach JR, Park J, Kang SW. Sleep Transcutaneous vs. End-Tidal CO_2 Monitoring for Patients with Neuromuscular Disease. Am J Phys Med Rehabil. 2015 Jul 1.	Outcomes
Yarchi D, Cohen A, Umansky T, Sukhotnik I, Shaoul R. Assessment of end-tidal carbon dioxide during pediatric and adult sedation for endoscopic procedures. Gastrointest Endosc. 2009 Apr;69(4):877-82.	Study type
Yazigi A, Zeeni C, Richa F, Chalhoub V, Sleilaty G, Noun R. The accuracy of non-invasive nasal capnography in morbidly obese patients after bariatric surgery. Middle East J Anesthesiol. 2007 Oct;19(3):483-94.	Population
Young A, Marik PE, Sibole S, Grooms D, Levitov A. Changes in end-tidal carbon dioxide and volumetric carbon dioxide as predictors of volume responsiveness in hemodynamically unstable patients. J Cardiothorac Vasc Anesth. 2013 Aug;27(4):681-4.	Outcomes
Zadel S, Strnad M, Prosen G, Mekis D. Point of care ultrasound for orotracheal tube placement assessment in out-of hospital setting. Resuscitation. 2015 Feb;87:1-6, 2015 Feb.:-6.	Outcomes
Zhang C, Wang M, Wang R, Wang W. Accuracy of end-tidal CO_2 measurement through the nose and pharynx in nonintubated patients during digital subtraction cerebral angiography. J Neurosurg Anesthesiol. 2013 Apr;25(2):191-6.	Population
Zongming J, Zhonghua C, Xiangming F. Sidestream capnographic monitoring reduces the incidence of arterial oxygen desaturation during propofol ambulatory anesthesia for surgical abortion. Med Sci Monit. 2014;20:2336-42.	Population

APPENDIX 7: Detailed Study Characteristics

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

Table 18: Study Characteristics for the Included Randomized Controlled Studies for Adult Patients Undergoing Procedural Sedation

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Klare 2016[51] Germany RCT	N = 242 **Inclusion criteria:** – age > 18 years – outpatients and in-patients – scheduled for ERCP – written informed consent **Exclusion criteria:** – ASA class V – pregnancy – pre-existing hypoxemia (SaO_2 < 90%) – hypotension (SBP < 90 mm Hg) – bradycardia (HR < 50/min)	Three endoscopy centres	**Procedure type:** ERCP **Sedative type:** propofol and midazolam **Sedative performed by:** A physician with experience in intensive care medicine	Standard monitoring + Capnography monitor (Capnostream 20 monitor, Oridion Medical) **visible** to the treatment team for assessment of ventilation.	Standard monitoring + Capnography monitor (Capnostream 20 monitor, Oridion Medical) **not visible** to the treatment team for assessment of ventilation.	**Primary outcome:** 1. Hypoxemia **Secondary outcomes:** 1. Apnea 2. Vital signs (hypotension - SBP < 90 mm Hg; bradycardia - HR < 50/min) 3. Procedural parameters (sedative dose, duration of procedure) 4. Patient satisfaction 5. Patient cooperation
Van Loon 2014[61] Netherlands RCT	N = 427 **Inclusion criteria:** – women undergoing minor gynecological procedures – age ≥ 18 years – undergoing deep sedation in an outpatient clinic **Exclusion criteria:** – ASA classes III to V	Outpatient clinic in the University Medical Centre	**Procedure type:** Gynecology procedures (procedures not listed but most of the procedures were abortions) **Sedative type:** Propofol Alfentanil **Sedation performed by:** nurses trained in sedation	Standard monitoring + Capnography monitor **visible** (Capnostream 20, Oridion medical) to the treatment team.	Standard monitoring	**Primary outcome:** 1. Hypoxemia **Secondary outcomes:** 1. Profound hypoxemia 2. Prolonged hypoxemia 3. Administration of supplemental oxygen 4. Airway interventions 5. Arousal or movement of the patient that interfered with

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	– allergic reactions to propofol, allergic reactions to soy or egg protein – sleep apnea syndrome		management; doctors with similar training in sedation management provided supervision.			performing the procedure 6. Early termination of the procedure
Friederich-Rust 2014[20] Germany RCT	N = 539 **Inclusion criteria:** – Age ≥ 18 years – Sedation requested during colonoscopy **Exclusion criteria:** – ASA class IV or V – Pregnant or breastfeeding – Contraindication for colonoscopy – Allergic to propofol, peanuts, soya products, chicken egg protein, sulfite	Endoscopy unit at a university hospital or endoscopy outpatient clinic	**Procedure type:** Colonoscopy only Colonoscopy + gastroscopy **Sedative type:** Propofol only Propofol + midazolam Propofol + ketamine Propofol + midazolam + ketamine **Sedation performed by:** Anesthesiologist* Nurse Internal medicine physician	Standard monitoring + capnography **visible** (Microcap, Oridion Capnography Inc. Needham MS, US)	Standard monitoring	**Primary outcome:** 1. Hypoxemia **Secondary outcomes:** 1. Severe hypoxemia 2. Increase of oxygen supplementation 3. Apnea 4. Time between apnea and hypoxemia 5. Assisted ventilation 6. Bradycardia
Slagelse 2013[48] Denmark RCT	N = 591 **Inclusion criteria:** – Age ≥ 18 years – Undergoing endoscopy – Compliant to nurse-administered propofol sedation criteria **Exclusion criteria:** – ASA physical status classification > III – Sleep apnea – Soy, egg, peanut allergy – BMI > 35 kg/m^2	Endoscopy department	**Procedure type:** Upper endoscopy Lower endoscopy **Sedative type:** Propofol **Sedation performed by:** Nurses	Standard monitoring + capnography **visible** (Phillips MP20 monitor; micro stream Capnography)	Standard monitoring	**Primary outcome:** 1. Hypoxia **Secondary outcomes:** 1. Actions taken to restore normal ventilation

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	– Mallampati score ≥ 4 – Acute gastrointestinal bleeding – Subileus – Gastric retention – Severe cold (30% ≤ FEV_1 < 50%).					
Beitz 2012[38] Germany RCT	N = 760 **Inclusion criteria:** - Age ≥ 18 years - Presenting for inpatient or outpatient colonoscopy **Exclusion criteria:** – ASA class IV and V – Allergic to propofol or tape and adhesives – Pregnancy – Pre-existing hypotension (SBP < 90 mm Hg) – Pre-existing bradycardia (HR < 50/min) – Hypoxemia (SaO_2 < 90%) – Need for oxygen supplementation due to pre-existing disease.	Endoscopy unit	**Procedure type:** Colonoscopy **Sedative type:** Propofol **Sedation performed by:** Gastroenterologist	Standard monitoring + Capnography monitor **visible** (Capnostream 20, Oridion medical) to the treatment team.	Standard monitoring + Capnography monitor **not visible** to the treatment team.	**Primary outcome:** 1. oxygen desaturation **Secondary outcomes:** 1. Apnea 2. abnormal ventilation 3. Hypoxemia 4. Severe hypoxemia 5. Increased oxygen supplementation 6. Assisted ventilation 7. Bradycardia 8. Hypotension 9. Patient cooperation 10. Patient satisfaction 11. Recovery time
Deitch 2010[19] US RCT	N = 132 **Inclusion criteria:** – Age ≥ 18 years – Required propofol sedation **Exclusion criteria:** – COPD	Emergency department at a 600-bed teaching hospital	**Procedure type:** Abscess incision and drainage Fracture reduction Joint reduction **Sedative type:** Propofol	Standard monitoring + Capnography monitor **visible** (Capnostream 20, Oridion medical) to the treatment team.	Standard monitoring + Capnography monitor **not visible** to the treatment team.	Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Hypoxia 2. Respiratory

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	– Chronic oxygen requirements – Hemodynamic instability – Pregnancy – Allergy to propofol, morphine, or fentanyl (or other components of its formulation) – Procedural sedation could compromise patient safety		**Sedation performed by:** Treating physicians in the emergency department			depression 3. Hypoventilation 4. Hypoxemia
Qadeer 2009[54] US RCT	N = 263 **Inclusion criteria:** – Age ≥ 18 years – Patients undergoing ERCP or EUS in an inpatient or outpatient setting – ASA class I to III **Exclusion criteria:** – ASA class IV to V – Required emergency procedures – Required monitored anesthesia care sedation – Used oxygen or non-invasive ventilation devices – Allergies to fentanyl, meperidine or midazolam	Endoscopy unit (in-patient or outpatient)	**Procedure type:** ERCP EUS) **Sedative type:** Midazolam + meperidine or fentanyl (diazepam was provided when patients were difficult to sedate with the indicated sedation regimen) **Sedation performed by:** staff physician (endoscopist assessed the depth of sedation)	Standard monitoring + Capnography-based signal (Capnostream 20, Oridion Capnography Inc.) from an independent observer indicating that the patient is “not breathing properly”. Capnography was not visible by the treating team.	Standard monitoring + Capnography-based signal (Capnostream 20, Oridion Capnography Inc.) only when apnea lasts more than 30 seconds (for safety purposes). Capnography was not visible by the treating team.	**Primary outcome:** 1. Hypoxemia **Secondary outcomes:** 1. Severe hypoxemia 2. Requirement of supplemental oxygen 3. Apnea 4. Abnormal ventilation

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ERCP = endoscopic retrograde cholangiopancreatography; $ETCO_2$ = end-tidal carbon dioxide; EUS = endoscopic ultrasonography; FEV_1 = forced expiratory volume in 1 second; HR = heart rate; min = minute; RCT = randomized controlled trial; $SaO_{2\,=}$ oxygen saturation; SBP = systolic blood pressure.

Table 19: Study Characteristics for the Included Non-randomized Studies for Adult Patients Undergoing Procedural Sedation

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Barnett 2016[52] US Prospective cohort study (before and after the implementation of capnography)	N = 966 **Inclusion criteria:** – Outpatients – Undergoing routine colonoscopy (during the specified time frames) – Moderate sedation (with fentanyl and midazolam) – Sufficient understanding of English for the completion of the survey – Room air insufflation **Exclusion criteria:** – Patients undergoing esophagogastroduodenoscopy	Endoscopy unit	**Procedure type:** Colonoscopy **Sedation type:** midazolam and fentanyl **Provider of sedation:** Unclear (nurses are the only health care provider mentioned in the study)	Standard monitoring + capnography (no device details provided)	Standard monitoring	Primary and secondary outcomes were not explicitly stated. **Outcomes**: 1. Patient comfort 2. Patient satisfaction 3. Quality of sedation 4. Patient discomfort 5. Oxygen desaturation < 90% or leading to intervention 6. SBP < 90 or > 160 mm Hg 7. HR < 50 or > 120 BPM 8. Hemodynamic or respiratory conditions (that interrupted the procedure) 9. Use of narcotics or reversal drugs 10. Hospitalization (due to sedation-related AE) 11. Usefulness of capnography
Tanaka 2014[56] US Prospective Cohort	N = 21 **Inclusion criteria:** – ASA I to III – Age ≥ 18 years – Scheduled to undergo sedation with local or regional anesthesia	Unclear	**Procedure type:** Knee replacement surgery Tumour bone resection Wrist open reduction **Sedation type:** IV Midazolam and	All patients received standard of care (including $ETCO_2$ monitoring) plus additional study monitors (capnography, brain function monitor, acoustic monitor) that were **not visible** to the treating clinicians (Capnostream 20, Oridion Capnography, Inc.; Pulse CO-Oximeter with Rainbow		Primary and secondary outcomes were not explicitly stated. **Outcomes:** Agreement between capnography and acoustic monitoring for

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	Exclusion criteria: – Not reported		Fentanyl **Provider of Sedation:** Anesthesiologist or regional anesthesia team	Acoustic Monitoring (Rad-87, software v. 7805, Masimo Corp., Irvine CA, US). Waveform and sound files from the capnography and acoustic monitors were retrospectively analyzed.		respiratory rate; accuracy of respiratory pause detection.
Schlag 2013[59] Germany Prospective Cohort	N = 20 **Inclusion criteria:** – Age ≥ 18 years – Undergoing percutaneous transhepatic cholangiodrainage with sedation **Exclusion criteria:** – Age < 18 years – ASA class V – Allergic to narcotic drugs – Pregnant – Pre-existing hypotension (systolic blood pressure < 90 mm Hg) – Bradycardia (HR < 50 BPM) – Hypoxemia (SaO_2 < 90%)	Endoscopy unit of an academic centre	**Procedure type:** Percutaneous transhepatic cholangiodrainage **Sedation type:** midazolam (IV) and 1% propofol (IV) **Provider of Sedation:** Physician with experience in intensive care medicine and resuscitation	All patients received standard monitoring + capnography (Capnostream 20, Covidien, US) that was **not visible** to the treating clinicians. Capnography data were analyzed by an independent observer who was not involved in the procedure		**Primary outcome:** 1. Duration of detected apnea **Secondary outcomes:** 1. Apnea 2. Oxygen desaturation 3. Hypoxemia 4. Bradycardia 5. Hypotension 6. Assisted ventilation 7. Number of complications 8. Examiner and patient satisfaction with sedation 9. Recovery time after sedation
Kusunoki 2012[60] Japan Prospective Cohort	N = 20 **Inclusion criteria:** – Adults – Undergoing ESD **Exclusion criteria:** – COPD – ASA class IV or V physical status	University hospital	**Procedure type:** ESD for superficial esophageal cancer ESD for early gastric cancer **Sedation type:** IV midazolam and pentazocine (2 received diazepam and haloperidol)	All patients were monitored with transcutaneous capnography (every 3 seconds, TOSCA 500, Radiometer Basel AG, Basel, Switzerland) and end-tidal capnography (every 5 seconds, Microcap Plus, Oridion Medical Ltd., Needham, MA, US) simultaneously. Recorded data were compared with each other, and compared		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Agreement between $PTCO_2$ and $ETCO_2$ 2. Hypoxia

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
			Provider of Sedation: Unclear	with respiratory rate and SpO_2, which were also monitored using the capnography device.		
De Oliveira 2010[53] US Prospective Cohort	N = 40 **Inclusion criteria:** – Women scheduled for hysteroscopy under monitored anesthesia care – Age > 18 years **Exclusion criteria:** – Age < 18 years – Unwilling to participate – History of lung disease – History of obstructive sleep apnea	Unclear	**Procedure type:** Hysteroscopy **Sedation type:** Not reported **Provider of sedation:** Anesthesia resident or certified registered nurse anesthetist, under the supervision of a faculty attending anesthesiologist	All patients were monitored with transcutaneous capnography (TOSCA 500, Radiometer America Inc., Westlake, OH, US) and $ETCO_2$ (Capnomac Ultima, Datex-Ohmeda, Madison, WI, US) once the patient reached a Ramsay score ≥ 5. Clinicians were blinded to the transcutaneous capnography monitor values, but $ETCO_2$ values were visible. Data were recorded by an independent observer and compared with each other.		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Agreement between $PTCO_2$ and $ETCO_2$ 2. Hypoventilation
Cacho 2010[62] Spain Prospective Cohort	N = 50 **Inclusion criteria:** – Age ≥ 18 years – Undergoing colonoscopy **Exclusion criteria:** – Age < 18 years – Mechanical ventilation – History of allergy to sedation and/or analgesia drugs	Outpatient and in-patient	**Procedure type:** Colonoscopy **Sedative type:** Pethidine + midazolam Propofol Propofol + fentanyl + midazolam **Provider of sedation:** Endoscopist and anesthetist oversaw patient sedation; a nurse administered the sedative and analgesics based on direction from the endoscopist.	All patients were monitored by clinical observation as well as with pulse oximetry (Nonin 8600, Medical Inc., Minnesota) and capnography (Microcap, Isso SA. Madrid, Spain) by a nurse beside the patient. Data were compared with each other; however, it is unclear how data were recorded.		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Hypoventilation 2. Apnea

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Deitch 2008[55] US Prospective cohort (underlying study was an RCT)	N = 110 **Inclusion criteria:** – Age > 18 years – Receiving propofol for a painful procedure **Exclusion criteria:** – COPD – Long-term oxygen use – Hemodynamic instability – Respiratory distress – Pregnancy – Allergy to study drugs	Emergency department at a Level I trauma centre medical centre (approximately 75,000 patient visits annually)	**Procedure type:** Abscess incision and drainage Fracture reduction Joint reduction **Sedative type:** Propofol **Provider of sedation:** The provider of sedation was not explicitly stated. However, emergency department personnel were involved in the procedure.	All patients were monitored for vital signs, oxygen saturation and capnography. The treatment team was blinded to $ETCO_2$ levels. A research assistant recorded $ETCO_2$ and waveform display data, as well as the treatment team's ability to recognize respiratory depression. These data were compared with each other.		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Respiratory depression 2. Adverse events
Deitch 2007[57] US Prospective cohort (underlying study was an RCT)	N = 80 **Inclusion criteria:** – Age > 2 years – Receiving fentanyl and midazolam for a painful procedure **Exclusion criteria:** – Severe COPD – Long-term oxygen use – Hemodynamic instability – Respiratory distress – Pregnancy – Allergy to any of the study drugs	Emergency department at a Level I trauma centre medical centre (approximately 70,000 patient visits annually)	**Procedure type:** Abscess incision and drainage Fracture or joint reduction Other procedures **Sedative type:** Intravenous midazolam and fentanyl **Provider of sedation:** Emergency room physician (orders sedatives and analgesics and performs the procedure) and emergency room	All patients were monitored for vital signs, oxygen saturation, and capnography. The treatment team was blinded to $ETCO_2$ levels. A research assistant recorded $ETCO_2$ and waveform display data, as well as the treatment team's ability to recognize respiratory depression. These data were compared with each other.		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Respiratory depression 2. Adverse events

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
			nurse (administers the drugs and monitors the patient)			
Burton 2006[58] US Prospective Cohort	N = 59 **Inclusion criteria:** - Adult and pediatric ED patients - Undergoing procedural sedation and analgesia **Exclusion criteria:** - Study investigators not present for enrolment.	ED of a 500-bed tertiary-care hospital with an ED volume of 52,000 patients per year	**Procedure type:** Dislocation reduction, shoulder Dislocation reduction, hip Fracture reduction Cardioversion Wound closure Transesophageal echocardiography Tube thoracostomy Disimpaction Foreign body removal **Sedative type:** Propofol Etomidate Midazolam Ketamine **Provider of sedation:** unclear: "performed in a fashion consistent with generally accepted guidelines"	All patients were monitored according to sedation guidelines + capnography (multi-parameter monitor (LIFEPAK 12 defibrillator/ monitor series, Medtronic Emergency Response Systems, Redmond, WA). The treatment team was blinded to study monitoring data. A study investigator recorded all monitoring data and observations. These data were compared with each other.		Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Clinically important acute respiratory events
Soto 2005[50] US Prospective Cohort	N = 99 **Inclusion criteria:** - Scheduled to undergo a procedure with monitored anesthesia care or sedation - Completion of a consent form	Large teaching institution (unit or department not specified)	**Procedure type:** Orthopedic, vascular, pain, and gastroenterology procedures. **Sedative type:** Most patients received	All patients were monitored with capnography (NPB-70 hand-held capnometer, Nellcor, Pleasanton), BIS, ECG, SpO_2, and blood pressure every 2.5 minutes. If a patient was experiencing apnea or airway obstruction for 60 seconds, the capnography notified (uncertain if it was an		Primary and secondary outcomes were not explicitly stated. **Outcomes**: 1. Deepest level of sedation achieved 2. Apnea

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	Exclusion criteria: - Pregnant - Age < 18 years - Unable to maintain an SpO_2 > 88% on room air **Note**: Patients were excluded from study after enrolment if they: - needed an artificial airway to maintain ventilation - needed artificial ventilation		combinations of midazolam, propofol and fentanyl **Provider of sedation:** anesthesia residents and nurse anesthetists (supervised by faculty anesthesiologists)	alarm or something else) the anesthesia provider of the event if the event was undetected by the standard monitoring. The anesthesia provider was blinded to both BIS and capnography data.		

AE = adverse event; ASA = American Society of Anesthesiologists; BIS = bispectral index; BPM = beats per minute; CA = California; ECG = electrocardiogram; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; ED = emergency department; ESD = endoscopic mucosal dissection; $ETCO_2$ = end-tidal carbon dioxide; HR = heart rate; IV = intravenous; $PTCO_2$ = transcutaneous carbon dioxide; RCT = randomized controlled trial; SBP = systolic blood pressure; SpO_2 = oxygen saturation measured by pulse oximetry; US = United States; WA = Washington

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Table 20: Study Characteristics for the Included Randomized Controlled Studies for Pediatric Patients Undergoing Procedural Sedation

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Langhan 2015[68] US RCT	N = 154 **Inclusion criteria:** - Children aged 1 to 20 years - Received IV medication to induce sedation **Exclusion criteria:** - Intubation - Administration of baseline supplemental oxygen without preceding hypoxemia - Conditions associated with abnormal $ETCO_2$ values, such as lower airway disease (e.g., asthma), diabetic ketoacidosis, moderate to severe dehydration, major trauma - Intolerance of the cannula - Crying for longer than 20% of sedation	Pediatric emergency department, urban, tertiary care academic centre	**Procedure type:** Fracture reduction Laceration repair Incision and drainage of abscess Arthrocentesis Dislocation Other **Sedative type:** Ketamine Midazolam **Sedation performed by:** Provider of sedation was not explicitly stated, although a nurse and physician certified to perform the sedation were present.	Standard monitoring + Capnography monitor (Nellcor OxiMax NPB-75 portable capnograph) **visible** to the treatment team.	Standard monitoring + Capnography monitor **not visible** to the treatment team.	**Primary outcomes:** 1. Hypoventilation without hyperventilation 2. Staff interventions 3. Oxygen desaturations **Secondary outcomes:** 1. Persistent hypoventilation 2. Timely interventions
Lightdale 2006[65] US RCT	N = 163 **Inclusion criteria:** - Patients undergoing elective procedures at an outpatient endoscopy unit - Age 6 months to 19 years - ASA class I to II	Endoscopy unit (outpatient) at a children's hospital	**Procedure type:** Endoscopy Colonoscopy **Sedative type:** Oral midazolam (some patients), intravenous midazolam, intravenous fentanyl	Standard monitoring + Capnography-based signal (Philips M4 with Microstream CO_2, Oridion Medical Inc.) from an	Standard monitoring + Capnography-based signal (Philips M4 with Microstream CO_2, Oridion Medical Inc.) from an	**Primary outcome:** 1. Oxygen desaturation **Secondary outcome:** 1. Abnormal ventilation 2. Termination of the

First author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	Exclusion criteria: - ASA class III to V - Receiving general anesthesia - Required emergency procedures - Seizure disorder - Use of mood-altering or chronic pain medications		**Sedation performed by:** Provider of sedation was not explicitly stated, though an endoscopist was said to provide the oral midazolam where applicable.	independent observer indicated with a raised hand when capnography waveforms were absent for > 15 seconds. Capnography was not visible by the treating team.	independent observer indicated with a raised hand when capnography waveforms were absent for > 60 seconds. Capnography was not visible by the treating team.	procedure 3. Adverse events

ASA = American Society of Anesthesiologists; BP = blood pressure; BPM = beats per minute; $ETCO_2$ = end-tidal carbon dioxide; IV = intravenous; RCT = randomized controlled trial.
[a] If RCT, sample size is the number of patients randomized.

Table 21: Study Characteristics for the Included Non-randomized Studies for Pediatric Patients Undergoing Procedural Sedation

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure	Outcome Measures
Kannikeswaran 2011[67] US Prospective Cohort	N = 150 **Inclusion criteria:** - Children (ages 1 to 10 years) - With developmental disability - Outpatient - Undergoing a brain MRI that required sedation **Exclusion criteria:** - No developmental disability - Not a brain MRI	Imaging department at a tertiary-care children's hospital (free-standing centre); approximately 2,000 children undergo MRI with sedation per year.	**Procedure type:** None — diagnostic **Sedative type:** Pentobarbital Fentanyl Midazolam Chloral hydrate **Provider of sedation:** A team of emergency medicine physicians	All patients were monitored according to sedation guidelines + capnography (N-85 hand-held capnograph/pulse Oximeter, Nellcor Puritan Bennett Inc., Boulder, CO, US) at baseline and during sedation (Medrad 9500 MRI, Medrad Inc., Warrendale, PA, US). $ETCO_2$ values were visible by the clinical team but were not used for patient management. Capnography data were recorded by a research assistant every minute during patient sedation.	Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Hypoxia 2. Acute respiratory event

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure	Outcome Measures
	- Required general anesthesia - ASA ≥ 3 - Admitted to inpatient unit prior to the MRI - Had a condition that did not allow for use of a nasal cannula - Previous study enrolment				
Anderson 2007[66] US Prospective Cohort	N = 125 **Inclusion criteria:** - Age 2 to 17 years - Weight > 12 kg - ASA class I or II - Target fasting time for solids was 5 to 6 hours and 3 to 4 hours for liquids **Exclusion criteria:** - Airway abnormalities - Abnormalities of the cardiorespiratory, hepatic, renal or central nervous system - History of allergy or adverse reaction to propofol, opioids, eggs, soy	Tertiary pediatric hospital (annually 40,000 visits to the emergency department)	**Procedure type:** Forearm fracture reduction Tibia/fibula fracture reduction Humerus fracture reduction Elbow joint reduction Hip joint reduction Shoulder joint reduction **Sedative type:** Propofol **Provider of sedation:** Consisted of a sedation team: 1. Pediatric emergency physician (administered propofol); 2. Orthopedic surgeon (surgery); 3. Registered nurse (recorded vital signs, dose timing, interventions and sedation depth); 4. EMT for airway management assistance.	All patients were monitored continuously by capnography (Portable Capnocheck II, BCI Waukesha, WI) A research assistant recorded the timing and duration of interventions related to the $ETCO_2$ measure; it was unclear it the treating physicians were aware of the $ETCO_2$ measures.	Primary and secondary outcomes were not explicitly stated. **Outcomes:** 1. Adverse respiratory events 2. Apnea 3. Adverse airway events 4. Airway interventions

ASA = American Society of Anesthesiologists; CO = Colorado; CO_2 = carbon dioxide; EMT = emergency management technician; $ETCO_2$ = end-tidal carbon dioxide; kg = kilograms; MRI = magnetic resonance imaging; PA = Pennsylvania; US = United States; WI = Wisconsin.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

Table 22: Study Characteristics for the Included Non-Randomized Studies for Adult Patients Undergoing CPR

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure Intervention Group	Comparator Group	Outcome Measures
Chen 2015[1] Taiwan Retrospective Cohort	n= 1113 **Inclusion criteria:** - Adult patients - Alive in 2005 - Underwent an out-of-hospital cardiac arrest **Exclusion criteria:** - Patients who did not have documented chest compressions	Patients experiencing an out-of-hospital cardiac arrest (subsequently receiving care in medical centres, regional hospitals, local hospitals and clinics)	**Procedure type:** Cardiac arrests **Sedation type:** NA **Provider of sedation:** NA	Documented use of $ETCO_2$.	No documented use of $ETCO_2$.	Not explicitly stated; however, the following outcomes were assessed in the regression models: **Outcomes:** 1. Sustained ROSC 2. Survival to hospital discharge

CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; NA = not applicable; ROSC = return of spontaneous circulation.

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No data available.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition

Table 23: Study Characteristics for the Included Non-Randomized Studies for Adult Patients in Serious or Critical Condition

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure	Outcome Measures
Bhat 2014[69] US Retrospective Cohort	n = 169 **Inclusion criteria:** - In the ED for ≥ 2 hours post-intubation (boarding — i.e., waiting for a bed in ICU) - Were managed primarily by the ED team **Exclusion criteria:** - Do-not-resuscitate order - Primarily managed by the trauma team - Patients who underwent major surgery within six hours of intubation	ED of a large tertiary care hospital	**Procedure type:** Intubated patients spending at least 2 hours boarding in the ED **Sedation type:** Not reported **Provider of sedation:** Not reported	6 post-intubation interventions were variably performed in the ED (chest x-ray, orogastric tube, sedation within 30 minutes, arterial blood gas, appropriate tidal volume, $ETCO_2$) All data were retrospectively collected through chart review with patients classified as having received the intervention or not received the intervention.	Primary and secondary outcome measures were not explicitly stated. **Outcomes:** 1. Mortality 2. Ventilator-associated pneumonia
Silvestri 2005[70] US Prospective Cohort	n = 153 **Inclusion criteria:** - Patients arriving at a regional trauma centre ED who underwent out-of-hospital endotracheal intubation **Exclusion criteria:** - Pronounced dead in the out-of-hospital setting - Patients who arrived with bag valve–mask ventilation, - Cricothyrotomy, laryngeal mask airway, or Combitube airway device.	ED of a Level 1 trauma centre	**Procedure type:** NA (patients arriving at the ED having undergone intubation out of hospital) **Sedation type:** Not reported **Provider of sedation:** Not reported	$ETCO_2$ monitoring was used by paramedics at their own discretion following endotracheal intubation in out-of-hospital settings. Upon arrival at the ED, the use of $ETCO_2$ was determined and patients were classified as having been monitored by $ETCO_2$ or not monitored by $ETCO_2$.	**Primary outcome:** unrecognized misplaced endotracheal tube Secondary outcomes were not explicitly stated. **Other outcomes:** 1. Mortality 2. Discharge location 3. Neurological impairment

ED = emergency department; $ETCO_2$ = end-tidal carbon dioxide; ICU = intensive care unit; NA = not applicable; US = United States.

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Table 24: Study Characteristics for the Included Randomized Controlled Studies for Pediatric Patients in Serious or Critical Condition

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Kong 2013[71] US RCT	n = 50 **Inclusion criteria:** - Infants (with one of the following: gestational age < 34 weeks, prenatally diagnosed anomalies except airway or lung abnormalities) - Receiving positive pressure ventilation with CPAP or ETT **Exclusion criteria:** - Oligohydramnios (amniotic fluid index < 5) before week 28 - Suspected hypoplasia of the lungs - Congenital conditions (diaphragmatic hernia, airway anomalies, heart disease)	Labour and delivery unit at a medical centre, and adjacent resuscitation room	**Procedure type:** NA (newborns with a high risk of needing resuscitation) **Sedation type:** NA **Provider of sedation:** NA	$ETCO_2$ was monitored after delivery and the display was visible to the resuscitation team. The team was told to keep $ETCO_2$ levels between 40 mm Hg and 55 mm Hg by adjusting ventilation as required.	$ETCO_2$ was monitored after delivery and the display was covered so the resuscitation team could not see it. The team was told to adjust ventilation as required by clinical judgment.	**Primary outcome**: 1. Admission (to ICU — approx. 1 hour after birth) PCO_2 values outside of the 40 mm Hg to 60 mm Hg range. **Secondary outcomes:** 1. Duration of ventilation 2. Oxygen use at 36 weeks 3. Pneumothorax 4. Pulmonary interstitial emphysema intraventricular hemorrhage or periventricular leukomalacia 5. Systemic blood flow 6. Adjustment of ventilation variables (respiratory rate, positive inspiratory pressure or positive end-expiratory pressure) in the delivery room
Kugelman 2015[72] Israel RCT	n = 66 **Inclusion criteria** - Intubated with a double-lumen endotracheal tube - Receiving conventional ventilation - Signed informed consent by a parent	In hospital University-affiliated tertiary care centre. Neonatal Intensive Care	**Procedure type:** N/A (ventilated infants in the neonatal intensive care unit) **Sedation type:** NA **Provider of sedation:** NA	Capnography data were recorded, visible to the treatment team, and used to guide patient care.	Capnography data were recorded. The capnography monitor was covered, but the capnograph tracing was	**Primary outcome:** 1. Time spent in a safe CO_2 range (> 30 mm Hg to < 60 mm Hg) Secondary outcomes were not explicitly stated.

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	- Expected to be able to provide 3 pairs of readings for PCO_2 and $ETCO_2$ **Exclusion criteria** - Intubated with a single-lumen ETT - Receiving high frequency ventilation	Units			visible to the medical team to ensure adequate measurements and to change the sampling line.	**Other outcomes:** 1. Changes in ventilation variables 2. Number and values of arterial blood gas measurements 3. number of red blood cell transfusions 4. Number of chest radiographs

CO_2 = carbon dioxide; CPAP = continuous positive airway pressure; ED = emergency department; $ETCO_2$ = end-tidal carbon dioxide; ETT = endotracheal tube; ICU = intensive care unit; NA = not applicable; PCO_2 = partial pressure of carbon dioxide; RCT = randomized controlled trial; US = United States.

Table 25: Study Characteristics for the Included Non-Randomized Studies for Pediatric Patients in Serious or Critical Condition

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Hawkes 2015[73] Ireland Prospective Cohort with historical control	n = 92 **Inclusion criteria:** - Infants (< 32 weeks gestation) **Exclusion criteria:** - Oligohydramnios (amniotic fluid index < 5) - Congenital conditions	University maternity hospital	**Procedure type:** NA (preterm infants) **Sedation type:** NA **Provider of sedation:** NA	All infants were monitored with $ETCO_2$ once they were placed on the resuscitation table. Monitoring continued throughout the stabilization period. The entire period was also monitored with video. The medical team was told to obtain capnographic waveforms but not make adjustments based on the	A historical control group that did not receive $ETCO_2$ monitoring.	Primary outcome not explicitly stated. **Outcomes:** 1. Comparison between $ETCO_2$ and PCO_2 values. within the first 10min of life 2. Percentage of patients falling within the target PCO_2 range. 3. Number of patients intubated.

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
				capnometry values displayed.		

$ETCO_2$ = end-tidal carbon dioxide; NA = not applicable; PCO_2 = partial pressure of carbon dioxide

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

Table 26: Study Characteristics for the Included Randomized Controlled Studies for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
Hutchison 2008[32] US RCT	n = 54 **Inclusion criteria:** - Age > 18 years - Post-orthopedic surgery - Received a physician order for opioid analgesia - Opioid-naive - Breathing spontaneously (non-ventilated) - No diagnosis of sleep apnea - No CPAP device - Had at least one of the following characteristics: BMI ≥ 30, history of snoring, history in the PACU of one episode of a RR < 10 breaths/minute or a basal (continuous) dosage of IV opioid or	PACU of a hospital	**Procedure type:** TKR Bilateral TKR TKR with bone biopsy Hip replacement Shoulder repair **Sedation type:** Not reported **Provider of sedation:** Not reported	Patients were monitored continuously using the capnography device (Alaris $ETCO_2$ module) (Cardinal Health) with Microstream Smart CapnoLine capnography nasal cannula (Oridion)	Patients were monitored every 4 hours by observation or auscultation — assessing pulse oximetry and respiratory rate (standard oxygen cannula)	**Primary outcome:** Respiratory depression **Secondary outcomes:** 1. Pauses in breathing during sleep 2. Time in the PACU 3. Distance ambulated on the first post-operative day (measured by the physical therapist) 4. Morphine equivalent consumed (recorded for 36 hours) 5. Pain intensity (measured on a 10-point rating scale)

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure		Outcome Measures
				Intervention Group	Comparator Group	
	oral opioid) - Be able to report their measure of pain intensity **Exclusion criteria:** Not reported					

BMI = body mass index; CPAP = continuous positive airway pressure; $ETCO_2$ = end-tidal carbon dioxide; IV = intravenous; PACU = post-anesthesia care unit; RR = respiratory rate; TKR = total knee replacement; US = United States.

Table 27: Study Characteristics for the Included Non-Randomized Studies for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

First Author, Year, Country, Study Type	Sample Size (n)[a] and Patient Characteristics	Study Setting	Procedure Type (n, %); Sedative type (n, %) and Provider of Sedation	Study Procedure	Outcome Measures
Ramsay 2013[74] US Prospective Cohort	n = 33 **Inclusion criteria:** - Adult patients - Presenting to a post-anesthesia care unit following surgery **Exclusion criteria:** Not reported	Post-anesthesia care unit of an academic tertiary-care facility	**Procedure type:** Laparoscopic gastric bypass Laparoscopic gastric sleeve Laparoscopic cholecystectomy Herniorrhaphy Cystoscopy and ureteroscopy Other **Sedative Type**: Not reported **Provider of Sedation**: Not reported	All patients were monitored with pulse co-oximeter with rainbow acoustic monitoring technology (RAM) technology (Rad-87, version 7804, Masimo) and capnography (Smart CapnoLine adult CO_2 nasal sampling set with capnostream20 version 4.5, Oridion, Needham, MA.) Data were retrospectively reviewed and manually annotated.	Primary and secondary objectives were not explicitly stated. **Outcomes**: 1. Ventilatory pause 2. True positive 3. False negative 4. Reliability 5. Drop-outs 6. Lower-bound limits

CO_2 = carbon dioxide; US = United States.

Research Question 8: Clinical effectiveness of $ETCO_2$ monitoring for pediatric patients with known obstructive sleep apnea or receiving high doses of opioids in post-operative care

No data available.

APPENDIX 8: Details of the Capnography Devices

Table 28: Details Of The Capnography Devices Used in the Included Studies for Adult Patients Undergoing Procedural Sedation

Device	Sidestream	Portable	Hand-held	Sampling Line	Technology	Monitored parameters	Population
Capnostream 20[19,38,51,54,56,59,61] (Covidien)	Yes	Yes	No	Smart CapnoLine Plus[19,38,59,61] Standard nasal cannula[56] Smart bite bloCO$_2$ (suitable for endoscopic procedures)[54] Smart CapnoLine Guardian[51]	Microstream	ETCO$_2$, RR, SpO$_2$	Neonate, pediatric and adult
Microcap, Oridion Capnography Inc. Needham Massachusetts, US[20,60] Microcap, Isso SA. Madrid, Spain[62]	Yes	Yes	Yes	Smart CapnoLine Plus[20] Oral and nasal cannula[62] Smart bite bloCO$_2$[60]	Microstream	ETCO$_2$, RR	Neonate, pediatric and adult
LIFEPAK 12 defibrillator/monitor series; Medtronic Emergency Response Systems, Redmond WA)[58]	Yes	Unknown	Unknown	Oral and nasal cannula[58]	Microstream	ETCO$_2$, HR, RR, SpO$_2$	Pediatric and adult
Capnomac Ultima[a], Datex-Ohmeda, Madison, WI, US[53]	Yes	Yes	No	Nasal cannula[53]	Unknown	CO$_2$, O$_2$, N$_2$O, RR, SpO$_2$	Pediatric and adult
Nellcor OxiMax NPB-75[55,57]	Yes	Yes	Yes	Smart CapnoLine [55,57]	Microstream	ETCO$_2$, SpO$_2$, pulse rate	Neonate, pediatric and adult
Nellcor OxiMax NPB-70[50]	Yes	Yes	Yes	Type of sampling line not specified[50]	Microstream	ETCO$_2$, RR	Neonate, pediatric and adult
Phillips MP20 monitor[48]	Yes	Yes	No	Smart CapnoLine Guardian[48]	Microstream	ECG, BP, SpO$_2$, temperature, BIS, cardiac output	Neonate, pediatric and adult

BIS = bioelectric impedance spectroscopy; BP = blood pressure; CO$_2$ = carbon dioxide; ECG = electrocardiogram; ETCO$_2$ = end-tidal carbon dioxide; HR = heart rate; N2O = nitrous oxide; O$_2$= oxygen; RR = respiratory rate; SpO$_{2\,=}$ arterial oxygen saturation measured by pulse oximetry.
[a] Retired model.

Table 29: Details of the Capnography Devices Used in the Included Studies for Pediatric Patients Undergoing Procedural Sedation

Device	Sidestream	Portable	Hand-held	Sampling Line	Technology	Multi-parameter Monitor	Population
Phillips MP20 monitor[65]	Yes	Yes	No	Smart MAC-Line O_2 $ETCO_2$ sampling lines[65]	Microstream	ECG, BP, SpO_2, temperature, BIS, cardiac output	Neonate, pediatric and adult
Capnocheck II[66]	Yes	Yes	Yes	Nasal cannula[66]	Not stated	$ETCO_2$, RR, SpO_2, HR	Pediatric and adult
N-85 hand-held capnograph/pulse oximeter (Nellcor Puritan Bennett Inc., Boulder, CO, US).[67]	Yes	Yes	Yes	Smart CapnoLine [67]	Microstream	CO_2, $ETCO_2$, SpO_2, Pulse rate, RR	Neonate, pediatric and adult
Nellcor OxiMax NPB-75[68]	Yes	Yes	Yes	Smart CapnoLine Plus[68]	Microstream	$ETCO_2$, SpO_2, pulse rate	Neonate, pediatric and adult

BIS = bioelectric impedance spectroscopy; BP = blood pressure; CO_2 = carbon dioxide; ECG = electrocardiogram; $ETCO_2$ = end-tidal carbon dioxide; HR = heart rate; N2O = nitrous oxide; O_2= oxygen; RR = respiratory rate; SpO_2 = arterial oxygen saturation measured by pulse oximetry.

Table 30: Details of the Capnography Devices Used in the Included Studies for Pediatric Patients in Serious or Critical Condition

Device	Sidestream	Portable	Hand-held	Sampling Line	Technology	Monitored parameters	Population
NICO Respiratory Profile Monitor (Respironics Inc, Andover Massachusetts) [71] PediCap (Nellcor Puritan Bennett, Pleasanton, California)	No (Mainstream)	NR	NR	N/A (device applied between the face mask or endotracheal tube and the T-piece resuscitator)[71]	NR	Multi-parameter model	NR
Philips Intellivue monitor (Philips Healthcare, Massachusetts, US)[73]	Yes	Yes	NR	Sampling line not specified.[73]	Microstream	Multi-parameter model (specific Intellivue device was not stated)	NR
Capnostream 20p[72] (Covidien Respiratory and Monitoring Solutions)	Yes	Yes	No	Sampling line not specified, but were supplied by Covidien.[72]	Microstream	$ETCO_2$, RR, SpO_2	Adult, pediatric and neonate

$ETCO_2$ = end-tidal carbon dioxide; NR = not reported; RR = respiratory rate; SpO_2 = arterial oxygen saturation measured by pulse oximetry.

APPENDIX 9: Detailed Patient Characteristics

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

Table 31: Patient Characteristics for the Included Randomized Controlled Studies for Adult Patients Undergoing Procedural Sedation

	Klare 2016[51]	Van Loon 2014[61]	Friederich-Rust 2014[20]	Slagelse 2013[48]	Beitz 2012[38]	Deitch 2010[19]	Qadeer 2009[54]
Mean Age in Years (SD)							
Intervention	62.2 (14.2)	24 (21 to 30)	52 (15)	59.1 (16.5)	58 (16.4)	31 (18 to 72)	60.8 (14.4)
Comparator	61.7 (14.9)	24 (21 to 30)	55 (15)	59.3 (15.9)	57.8 (16.6)	37 (18 to 88)	60.6 (14.3)
Sex (% Male)							
Intervention	57.9%	0%	49%	66.0%	50.4%	58.8%	49.2%
Comparator	48.7%	0%	51%	66.6%	54.5%	48.5%	50.4%
BMI (kg/m^2)							
Intervention	25.1 (3.8)	23.4 (3.3)	25 (5)	24.7 (4.2)	25.6 (4.6)	NR	26.5 (5.8)
Comparator	25.5 (4.7)	23.3 (3.8)	25 (4)	24.4 (4.1)	25.9 (5.3)	NR	26.2 (5.6)
Smoking Status							
Intervention							
Current	57 (54.8)	NR	57 (21)	NR	160 (41.8)	NR	22 (17.9)
Former		NR	30 (11)	NR		NR	12 (9.8)
Never		NR	180 (67)	NR	NR	NR	89 (72.4)
Comparator							
Current	56 (47.9)	NR	57 (21)	NR	179 (47.9)	NR	23 (19.3)
Former		NR	30 (11)	NR		NR	16 (13.5)
Never		NR	179 (67)	NR	NR	NR	80 (67.2)
Comorbid Conditions							
Intervention							
CVD	NR	NR	104 (39)	NR	NR	NR	NR
Heart disease	37 (30.6)	NR	NR	NR	77 (20.1)	NR	29 (23.4)
Lung disease	13 (10.7)	NR	NR	NR	28 (7.3)	NR	8 (6.5)

	Klare 2016[51]	Van Loon 2014[61]	Friederich-Rust 2014[20]	Slagelse 2013[48]	Beitz 2012[38]	Deitch 2010[19]	Qadeer 2009[54]
COPD	NR	NR	35 (13)	NR	NR	NR	NR
Sleep apnea	1 (0.8)	0	9 (3)	0	10 (2.6)	NR	14 (11.3)
Regular narcotic use	18 (14.9)[a]	NR	22 (8)	NR	NR	NR	36 (29.0)
Regular benzodiazepine use		NR	NR	NR	NR	NR	25 (20.3)
Comparator							
CVD	NR	NR	101 (38)	NR	NR	NR	NR
Heart disease	26 (22.2)	NR	NR	NR	76 (20.3)	NR	27 (22.0)
Lung disease	10 (8.5)	NR	NR	NR	47 (12.6)	NR	13 (10.6)
COPD		NR	32 (12)	NR	NR	NR	NR
Sleep apnea	2 (1.7)	0	11 (4)	0	17 (4.5)	NR	16 (13.0)
Regular narcotic use	14 (12.0)[a]	NR	17 (6)	NR	NR	NR	30 (24.4)
Regular benzodiazepine use		NR	NR	NR	NR	NR	21 (16.9)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.
[a] Reported as "regular narcotic or sedative use."

Table 32: Details of Procedure and Sedation for the Included Randomized Controlled Studies for Adult Patients Undergoing Procedural Sedation

Intervention	Comparator
Procedure Type n (%)	
Klare 2016[51]	All procedures were ERCP	All procedures were ERCP
Van Loon 2014[61]	Most of the procedures were abortions[a]	Most of the procedures were abortions[a]
Friederich-Rust 2014[20]	Colonoscopy only: 177 (66) Colonoscopy + gastroscopy: 90 (34)	Colonoscopy only: 183 (69) Colonoscopy + gastroscopy: 83 (31)
Slagelse 2013[48]	Upper endoscopy: 121 (43.6) Lower endoscopy: 156 (59.4)	Upper endoscopy: 134 (50.9) Lower endoscopy: 129 (49.1)
Beitz 2012[38]	All patients underwent colonoscopy.	All patients underwent colonoscopy.
Deitch 2010[19]	Abscess incision and drainage: 32 (47)	Abscess incision and drainage: 27 (43)

Intervention		Comparator
	Fracture reduction: 8 (12) Joint reduction: 28 (41)	Fracture reduction: 11 (17) Joint reduction: 26 (40)
Qadeer 2009[54]	ERCP: 33 (26.6) EUS: 91 (73.4)	ERCP: 32 (26.0) EUS: 91 (74.0)
Procedure Length; Mean Number Minutes (SD) Unless Otherwise Indicated		
Klare 2016[51]	median 38.0 (range 6 to 165)	median 38.0 (range 5 to 164)
Van Loon 2014[61]	19.3 (9.9)	18.9 (10.3)
Friederich-Rust 2014[20]	38 (16)	38 (17)
Slagelse 2013[48]	24 (13;31)[b]	23.6 (12;30)[b]
Beitz 2012[38]	35.9 (22.0)	33.8 (20.6)
Qadeer 2009[54]	37.2 (16.1)	34.4 (12.5)
Deitch 2010[19]	13 (3 to 29)[c]	14 (4 to 32)[c]
Sedative Type n (%)		
Klare 2016[51]	Propofol and Midazolam	Propofol and Midazolam
Van Loon 2014[61]	Propofol (all patients) Alfentanil also given: 6 (2.9)	Propofol (all patients) Alfentanil also given:5 (2.4)
Friederich-Rust 2014[20]	Propofol only: 69 (26) Propofol + midazolam: 92 (34) Propofol + ketamine:14 (5) propofol + midazolam + ketamine: 92 (34)	Propofol only: 83 (31) Propofol + midazolam: 77 (29) Propofol + ketamine: 9 (3) propofol + midazolam + ketamine: 97 (37)
Slagelse 2013[48]	Propofol (all patients)	Propofol (all patients)
Beitz 2012[38]	Propofol (all patients)	Propofol (all patients)
Qadeer 2009[54]	Midazolam + meperidine (n = NR) Midazolam + fentanyl (n = NR) (diazepam was added when patients were difficult to sedate; n = NR)	Midazolam + meperidine (n = NR) Midazolam + fentanyl (n = NR) (diazepam was added when patients were difficult to sedate; n = NR)
Deitch 2010[19]	Propofol (all patients)	Propofol (all patients)
Sedative Dose		
Klare 2016[51]	Midazolam: 2.5 mg (standard dose)	Midazolam: 2.5 mg (standard dose)

Intervention					Comparator			
	Propofol: median 400 mg (range 110 to 1610)				Propofol: median 390 mg Range 80 to 1,160)			
Van Loon 2014[61]	propofol: 14.9 (3.2) mg·kg−1·h−1				propofol: 15.3 (5.3) mg·kg−1·h−1			
Friederich-Rust 2014[20]	Propofol: 337mg (SD 140) Midazolam: 1.63mg (SD 0.79) Ketamine: 21 mg (SD 7)				Propofol: 338mg (SD 148) Midazolam: 1.54mg (SD 0.75) Ketamine: 20 mg (SD 7)			
Slagelse 2013[48]	352 mg (231;450)[b]				340 mg (220;410)[b]			
Beitz 2012[38]	197.9 mg (SD 137.4)				197.3 mg (SD 135.2)			
Qadeer 2009[54]	Meperidine (mg) or fentanyl (mcg): 126.2 (44.4) midazolam (mg) 6.2 (2.5) diazepam (mg): 3.5 (7.8)				Meperidine (mg) or fentanyl (mcg): 127.4 (40.7) midazolam (mg) 6.4 (2.4) diazepam (mg): 3.3 (8.0)			
Deitch 2010[19]	Mean total dose: 1.4 mg/kg (SD 0.43)				Mean total dose: 1.5 mg/kg (SD 0.56)			
Depth of Sedation								
Klare 2016[51]	NR				NR			
Van Loon 2014[61]	RSS 5[d]				RSS 5[d]			
Friederich-Rust 2014[20]	92% deep sedation				94% deep sedation			
Slagelse 2013[48]	NR				NR			
Beitz 2012[38]	NR[e]				NR[e]			
Qadeer 2009[54]	NR[f]				NR[f]			
Deitch 2010[19]	RSS 4 (1 to 6)[g]				RSS 4 (1 to 6)[g]			
Routine Administration of Supplemental Oxygen								
Klare 2016[51]	Yes				Yes			
Van Loon 2014[61]	No				No			
Friederich-Rust 2014[20]	Yes				Yes			
Slagelse 2013[48]	Yes				Yes			
Beitz 2012[38]	Yes				Yes			
Qadeer 2009[54]	No				No			
Deitch 2010[19]	Yes				Yes			
American Society of Anesthesiologists Class n (%)								
	class I	**class II**	**class III**	**class IV**	**class I**	**class II**	**class III**	**vlass IV**
Klare 2016[51]	19 (15.7)	53 (43.8)	45 (37.2)	4 (3.3)	21 (17.9)	53 (45.3)	37 (31.6)	6 (5.1)
Van Loon 2014[61]	171 (83.0)[h]	35 (17.1)	0	NR	172 (82.3)[h]	37 (17.7)	0	NR
Friederich-Rust 2014[20]	119 (45)	128 (48)	20 (8)	NR	116 (44)	138 (52)	12 (5)	NR
Slagelse 2013[48]	88 (33.6)	156 (59.5)	18 (6.9)	NR	86 (30.9)	171 (61.9)	20 (7.2)	NR

Intervention					Comparator			
Beitz 2012[38]	117 (30.5)	156 (40.7)	102 (26.6)	NR	113 (30.2)	156 (41.7)	99 (26.5)	NR
Qadeer 2009[54]	9 (7.3)	86 (69.4)	29 (23.4)	NR	9 (7.3)	86 (69.9)	28 (22.8)	NR
Deitch 2010[19]	NR	NR	NR	NR	NR	NR	NR	NR

ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasonography; mcg = micrograms; NR = not reported; RSS = Ramsay Sedation Scale; SD = standard deviation.
[a] Procedures not listed but text (study population in method section) states that most were surgical abortion.
[b] Median (25th; 75th percentiles).
[c] Median (range).
[d] Intended score.
[e] Study stated that they aimed to achieve adequate sedation.[38]
[f] Study stated that the randomization process was expected to balance the number of patients experiencing a deep level of sedation.
[g] Median Ramsay sedation score (range).
[h] The number of patients in ASA class I was calculated by CADTH (study excluded patients in ASA class III to V).

Table 33: Patient Characteristics for the Included Non-randomized Studies for Adult Patients Undergoing Procedural Sedation

	Barnett 2016[52]	Tanaka 2014[56]	Schlag 2013[59]	Kusunoki 2012[60]	De Oliveira 2010[53]	Cacho 2010[62]	Deitch 2008[55]	Deitch 2007[57]	Burton 2006[58]	Soto 2005[50]
Mean Age in Years (SD)										
Total Population	58.1 (21 to 88) in $ETCO_2$; 56.6 (18 to 87) in no $ETCO_2$	61.3 (SD 14.5 range 32 to 87)	62.5 (11.3)	70.1 (SD NR)	42 (SD 9; range 27 to 65)	56 (14.4)	37 (18 to 86)	NR (range 2 to 77)	38 (1 to 89)	51 (SD 13, range 19 to 78)
Sex (% Male)										
Total Population	50%	25%	60%	90%	0%	54%	44%	40%	58%	52%
BMI (kg/m^2)										
Total Population	27.4 (12.4 to 48.4) in $ETCO_2$ 27.6 (10.3 to 48.7) in no $ETCO_2$	31.6	21.9 (3.5)	NR	25 (SD 5; range 17 to 34)	NR	NR	NR	NR	NR

	Barnett 2016[52]	Tanaka 2014[56]	Schlag 2013[59]	Kusunoki 2012[60]	De Oliveira 2010[53]	Cacho 2010[62]	Deitch 2008[55]	Deitch 2007[57]	Burton 2006[58]	Soto 2005[50]
Smoking Status n(%)										
Total Population										
Current	101 (10)	NR	8 (40)	NR	NR	NR	NR	NR	NR	NR
Former	865 (90)	NR		NR	NR	History of smoking: 11 (22)	NR	NR	NR	NR
Never		NR	NR	NR	NR	NR	NR	NR	NR	NR
Comorbid conditions										
Total Population										
CVD	199 (21)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Heart disease	NR	NR	NR	NR	NR	8 (16)	NR	NR	NR	NR
Lung disease	79 (8)	NR	NR	NR	NR	NR	NR	NR	NR	NR
COPD	NR	NR	NR	0 (0)	NR	5 (10)	NR	NR	NR	NR
Sleep apnea	NR (may have been included in "lung disease")	NR	0	NR	NR	NR	NR	NR	NR	NR
Regular narcotic use	4 (0.4)	NR	1 (5.0)	NR	NR	1 (2)	NR	NR	NR	NR
Regular benzodiazepine use	NR	NR	NR	NR	NR	8 (16)	NR	NR	NR	NR

BMI = body mass index; COPD = chronic obstructive pulmonary disorder; CVD = cardiovascular disease; NR = not reported; SD = standard deviation.

Table 34: Details of Procedure and Sedation for the Included Non-randomized Studies for Adult Patients Undergoing Procedural Sedation

	Total Population
Procedure type n(%)	
Barnett 2016[52]	Colonoscopy; 966 (100)
Tanaka 2014[56]	Knee replacement surgery: 18 (90) Tumor bone resection: 1 (5) Wrist open reduction: 1 (5)
Schlag 2013[59]	Percutaneous transhepatic cholangiodrainage (all patients)

	Total Population
Kusunoki 2012[60]	ESD for superficial esophageal cancer: 2 ESD for early gastric cancer: 18
De Oliveira 2010[53]	NR
Cacho 2010[62]	Colonoscopy (all patients)
Deitch 2008[55]	Abscess incision and drainage: 69 (63) Fracture reduction: 15 (14) Joint reduction: 20 (18)
Deitch 2007[57]	Abscess incision and drainage: 50 (62.5) Fracture/joint reduction: 27 (33.75) Other procedures: 3 (3.75)
Burton 2006[58]	Dislocation reduction, shoulder: 10 (16) Dislocation reduction, hip: 7 (12) Fracture reduction: 18 (30) Cardioversion: 11 (18) Wound closure: 10 (16) Transesophageal echocardiography: 1 (2) Tube thoracostomy: 1 (2) Disimpaction 1 (2) Foreign body removal: 1 (2)
Soto 2005[50]	Orthopedic, vascular, pain, and gastroenterology procedures (specific percentages were not reported)
Procedure length	
Barnett 2016[52]	NR
Tanaka 2014[56]	NR
Schlag 2013[59]	NR
Kusunoki 2012[60]	174 (range, 72 to 589)
De Oliveira 2010[53]	NR
Cacho 2010[62]	Patients without disordered respiration: 20.6 (SD 9) Patients with disordered respiration: 20.3 (SD 9.6)
Deitch 2008[55]	NR
Deitch 2007[57]	NR
Burton 2006[58]	NR
Soto 2004[50]	NR
Sedation Type	
Barnett 2016[52]	midazolam and fentanyl
Tanaka 2014[56]	NR
Schlag 2013[59]	midazolam (IV) 1% propofol (IV)
Kusunoki 2012[60]	midazolam

	Total Population
	pentazocine (2 received diazepam and haloperidol)
De Oliveira 2010[53]	NR
Cacho 2010[62]	Pethidine + midazolam: 21 (42) Propofol: 8 (16) Propofol + fentanyl + midazolam: 21 (42)
Deitch 2008[55]	Propofol (all patients)
Deitch 2007[57]	IV midazolam and fentanyl
Burton 2006[58]	Propofol: 41 (68) Etomidate: 4 (7) Midazolam: 3 (5) Ketamine: 12 (20)
Soto 2005[50]	Most patients received combinations of the following: Midazolam: 83 (83) Propofol : 85 (85) Fentanyl: 35 (35)
Sedation Dose	
Barnett 2016[52]	Total fentanyl: mean 142.9 mcg (range 45 to 300)
Tanaka 2014[56]	NR
Schlag 2013[59]	total midazolam dose: 2.5mg (SD 0) total propofol dose: 274.3mg (SD 222.8)
Kusunoki 2012[60]	midazolam: 3.4 mg/h (2 to 55 mg/h) pentazocine: 18 mg (15 to 45 mg) 2 patients: 10 mg of diazepam and 5 mg of haloperidol
De Oliveira 2010[53]	NR
Cacho 2010[62]	NR
Deitch 2008[55]	NR
Deitch 2007[57]	Fentanyl dose(mcg): median NR; range 25 to 400 Midazolam dose(mg): median NR; range 0.5 to 10
Burton 2006[58]	NR
Soto 2005[50]	NR
Depth of Sedation	
Barnett 2016[52]	NR (Patients were said to be undergoing moderate sedation)
Tanaka 2014[56]	NR
Schlag 2013[59]	NR
Kusunoki 2012[60]	NR
De Oliveira 2010[53]	RSS ≥ 5
Cacho 2010[62]	NR
Deitch 2008[55]	Median RSS 90 sec after the last dose of the pre-procedure: 5 (2 to 6)

	Total Population			
Deitch 2007[57]	Median RSS 90sec after the last dose of the pre-procedure: 4 (2 to 5)			
Burton 2006[58]	NR[a]			
Soto 2005[50]	NR[b]			
Routine Administration of Supplemental Oxygen				
Barnett 2016[52]	Not clear			
Tanaka 2014[56]	Yes			
Schlag 2013[59]	Yes			
Kusunoki 2012[60]	Yes			
De Oliveira 2010[53]	Yes			
Cacho 2010[62]	Yes			
Deitch 2008[55]	No (received compressed room air or supplemental oxygen)			
Deitch 2007[57]	No (received compressed room air or supplemental oxygen)			
Burton 2006[58]	Yes			
Soto 2005[50]	Yes			
American Society of Anesthesiologists Class[c] n (%)				
	class I	**class II**	**class III**	**class IV**
Barnett 2016[52]	222 (23)	702 (73)	42 (4)	0
Tanaka 2014[56]	NR	NR	NR	NR
Schlag 2013[59]	0	7 (35.0)	12 (60.0)	1 (5.0)
Kusunoki 2012[60]	8 (40)	9 (45)	3 (15)	0
De Oliveira 2010[53]	NR	NR	NR	NR
Cacho 2010[62]	39 (78)		11 (22)	
Deitch 2008[55]	NR	NR	NR	NR
Deitch 2007[57]	NR	NR	NR	NR
Burton 2006[58]	NR	NR	NR	NR

ASA = American Society of Anesthesiologists; BIS = bispectral index; ESD = endoscopic submucosal dissection; IV = intravenous; mcg = micrograms; NR = not reported; RSS = Ramsay sedation score; SD = standard deviation.

[a] RSS measured and recorded but not reported.

[b] The majority of patients were in minimal or moderate sedation (87.8% of patients). The mean BIS for all patients was 77 (SD 14). Ranging from a mean of 62 (SD 22) for patients who experienced no apnea events in deep sedation to 88 (SD 6) for patients who did not experience apnea with minimal sedation.

[c] ASA class I: a normal healthy patient; ASA class II: a patient with mild and systemic disease; ASA class III: a patient with severe systemic disease; ASA class IV: a patient with severe systemic disease that is a constant threat to life.

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Table 35: Patient Characteristics for the Included Randomized Studies for Pediatric Patients Undergoing Procedural Sedation

	Langhan 2015[68]	Lightdale 2006[65]
Mean age in years (SD)		
Intervention	8.6 (5.1)	median: 14.8 (range 0.7 to 18.9)
Comparator	8.2 (4.8)	median: 14.1 (range 0.5 to 18.7)
Sex (% male)		
Intervention	59.7%	55%
Comparator	55.8%	54%
BMI (kg/m^2)		
Intervention	NR	NR
Comparator	NR	NR
Smoking Status		
Intervention	NR	NR
Comparator	NR	NR
Comorbid conditions		
Intervention	NR	NR
Comparator	NR	NR

BMI = body mass index; NR = not reported; SD = standard deviation.

Table 36: Details of Procedure and Sedation for the Included Randomized Controlled Studies for Pediatric Patients Undergoing Procedural Sedation

	Intervention	Comparator
Procedure Type n (%)		
Langhan 2015[68]	Fracture reduction: 43 (55.8) Laceration repair: 13 (16.9) Incision and drainage of abscess: 16 (20.8) Arthrocentesis: 2 (2.6) Dislocation: 1 (1.3) Other: 2 (2.6)	Fracture reduction: 42 (54.5) Laceration repair: 16 (20.8) Incision and drainage of abscess: 12 (15.6) Arthrocentesis: 3 (3.9) Dislocation: 4 (5.2) Other: 0 (0)
Lightdale 2006[65]	Endoscopy: 72 (87) Colonoscopy: 11 (13)	Endoscopy: 70 (88) Colonoscopy: 10 (13)
Sedative Type n (%)		
Langhan 2015[68]	Ketamine: 76 (98%) Midazolam: 32 (41.6%)	Ketamine: 75 (98%) Midazolam: 31 (40.3%)

	Intervention			Comparator		
Lightdale 2006[65]	IV midazolam, IV fentanyl; some patients received oral midazolam[a]			IV midazolam, IV fentanyl; some patients received oral midazolam[a]		
Procedure Length; Mean Number Minutes (SD) Unless Otherwise Indicated						
Langhan 2015[68]	36.9 (17.9)			35 (14.8)		
Lightdale 2006[65]	Endoscopy: 10 (0 to 24) Colonoscopy: 39 (34 to 67)			Endoscopy: 10 (4 to 25) Colonoscopy: 39 (15 to 69)		
Routine Administration of Supplemental Oxygen						
Langhan 2015[68]	No			No		
Lightdale 2006[65]	Yes			Yes		
Sedative Dose						
Langhan 2015[68]	ketamine (mg/kg): 1.45			ketamine (mg/kg): 1.32		
Lightdale 2006[65]	oral midazolam (mg/kg): 0 (0 to 0.5) IV midazolam (mg/kg): 0.14 (0.02 to 0.27) IV fentanyl (mg/kg): 2.0 (0.6 to 4.3)			oral midazolam (mg/kg): 0 (0 to 0.5) IV midazolam (mg/kg): 0.13 (0.02 to 0.32) IV fentanyl (mg/kg): 2.2 (0.8 to 4.2)		
Ramsay Sedation Scale Level (%)						
Langhan 2015[68]	NR			NR		
Lightdale 2006[65]	2: 16 (19) 3: 31 (37) 4: 36 (43)			2: 10 (12) 3: 35 (44) 4: 35 (44)		
ASA Sedation Class[b]						
	class I	**class II**	**class III**	**class I**	**class II**	**class III**
Langhan 2015[68]	75 (97.4)	2 (2.6)	0	73 (94.8)	3 (3.9)	1 (1.3)
Lightdale 2006[65]	66 (80)	17 (20)	0	67 (84)	13 (16)	0

ASA = American Society of Anesthesiologists; IV = intravenous; mcg = micrograms; NR = not reported; SD = standard deviation.
[a] Number not reported (0.5 mg/kg; maximum dose: 20 mg) in preparation for peripheral intravenous catheter placement.
[b] ASA class I: a normal healthy patient; ASA class II: a patient with mild and systemic disease; ASA class III: a patient with severe systemic disease.

Table 37: Patient Characteristics for the Included Non-randomized Studies for Pediatric Patients Undergoing Procedural Sedation

	Kannikeswaran 2011[67]	Anderson 2007[66]
Mean Age in Years (SD)		
Total Population	1 to 3 years: 64 (43%) 4 to 6 years: 48 (32%) 7 to 10 years: 38 (25%)	median: 8 (range 2 to 17)
Sex (% Male)		
Total Population	68%	NR

	Kannikeswaran 2011[67]	Anderson 2007[66]
BMI (kg/m^2)		
Total Population	NR	NR
Smoking Status n (%)		
Total Population	NR	NR
Comorbid Conditions		
Total Population	NR	NR

BMI = body mass index; NR = not reported; SD = standard deviation.

Table 38: Details of Procedure and Sedation for the Included Non-randomized Studies for Pediatric Patients Undergoing Procedural Sedation

	Total Population
Procedure type n(%)	
Kannikeswaran 2011[67]	Brain MRI: 100%
Anderson 2007[66]	Forearm fracture reduction: 88% Tibia/fibula fracture reduction: 6% Humerus fracture reduction: 2% Elbow joint reduction: 2% Hip joint reduction: 1% Shoulder joint reduction: 1%[a]
Procedure Length	
Kannikeswaran 2011[67]	NR
Anderson 2007[66]	NR
Sedation Type	
Kannikeswaran 2011[67]	Pentobarbital: 142 (94.7%) Fentanyl: 126 (84%) Midazolam: 29 (19.3%) Chloral hydrate: 4 (2.7%)
Anderson 2007[66]	Propofol: all patients
Sedation Dose	
Kannikeswaran 2011[67]	Pentobarbital (mg/kg): 4.58 (SD 1.38) Fentanyl (mcg/kg): 1.09 (SD 0.29) Midazolam (mg/kg): 0.26 (SD 0.11) Chloral hydrate (mg/kg): 99.8 (SD 0.50)
Anderson 2007[66]	2.8 mg/kg (range 0.7 to 9.6mg/kg)

	Total Population	
Ramsay Sedation Score		
Kannikeswaran 2011[67]	NR	
Anderson 2007[66]	median 6 (range 3 to 8) 5 patients reached a level of 8 at one assessment point	
Routine Administration of Supplemental Oxygen		
Kannikeswaran 2011[67]	No	
Anderson 2007[66]	No	
American Society of Anesthesiologists (ASA) Sedation Class[b] n (%)		
	class I	**class II**
Kannikeswaran 2011[67]	53 (35.3)	97 (64.7)
Anderson 2007[66]	NR (88)	NR (12)

ASA = American Society of Anesthesiologists; ESD = endoscopic submucosal dissection; IV = intravenous; mcg = micrograms; MRI = magnetic resonance imaging; NR = not reported; SD = standard deviation.
[a] Denominator not specified.
[b] ASA class I: a normal healthy patient; ASA class II: a patient with mild and systemic disease.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

Table 39: Patient Characteristics for the included Non-randomized Studies for Adult Patients Undergoing CPR

Study	Study Group	Number of Participants	Age (Mean, SD), % Male Sex, BMI	Intubation	Procedure Time	Baseline Respiration Rate	Other Variables
Chen 2015[1]	$ETCO_2$	53	68.9 years (SD 15.9) 50.9% male BMI: NR	NR	Mean CPR time: 27 min (SD 14)	NR	Coronary artery disease: 10 (18.9) Hypertension: 26 (49.1) Heart failure: 1 (1.9) Atrial fibrillation: 1 (1.9)
	Comparator	1,060	69.6 years (SD 16.7) 60.8% male BMI: NR	NR	Mean CPR time: 25 min (SD 16)	NR	Coronary artery disease: 200 (18.9) Hypertension: 521 (49.2) Heart failure: 19 (1.8) Atrial fibrillation: 16 (1.5)

BMI = body mass index; CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; min = minute; NR = not reported; SD = standard deviation.

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No data available.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical CCondition

Table 40: Patient Characteristics for the Included Non-randomized Studies for Adult Patients in Serious or Critical Condition

Study	Study Group	Number of Participants	Age (Mean, SD), % Male Sex; BMI	Intubation	Procedure Type	Baseline Respiration Rate	Number of Procedures
Bhat 2014[69]	Total	Entered: 169 Completed: 154	Age: NR Sex: NR	NR	NR	NR	NA
Silvestri 2005[70]	Intervention	Entered: 93 Completed: NR	41.4 (SD 26.4) 74%	100%	medical: 25 (26.9) trauma: 68 (73.1)	NR	NR
	Comparator	Entered: 60 Completed: NR	46.2 (SD 26.6) 63%	100%	medical: 24 (40) trauma: 36 (60)	NR	NR
	Total	Entered: 153 ITT: 153	Age: NR 69.9%	100%	medical: 49 (32) trauma: 104 (78)	NR	NR

BMI = body mass index; ITT = intention-to-treat; NR = not reported; SD = standard deviation.

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Table 41: Patient Characteristics for the Included Randomized Controlled Studies for Pediatric Patients in Serious or Critical Condition

Study	Study Group	Number of Participants	Gestational Age (Mean, SD), % Male Sex; Birth Weight	Respiratory Problems	Intubation	Caesarian Delivery; 5-Minute APGAR	Other
Kong 2013[71]	Intervention	Entering: 25 Completing: 24 Complete data available: 18	28.9 weeks (24.6 to 35.3) 75% 1,162 g (530 to 2235)	Pulmonary surfactant: 12 (50)	Delivery room: 3 (12.5) Neonatal ICU: 9 (37.5)	19 (79.2) 5 min Apgar < 5: 0 (0.0)	Cord arterial PCO_2: 52 mm Hg (37 to 83)
	Control	Entering: 25 Completing: 24 Complete data available: 19	29.3 weeks (24.9 to 35.1) 50% 1,151 g (500 to 2190)	Pulmonary surfactant: 13 (54.2)	Delivery room: 4 (16.7) Neonatal ICU: 10 (41.7)	17 (70.8) 5 min Apgar < 5: 1 (4.2)	Cord arterial PCO_2: 50 mm Hg (40 to 63)
	Total	Entering: 50 Completing: 48 Complete data available: 37	Age: NR 62.5% Weight: NR	Pulmonary surfactant: 25 (52.1)	Delivery room: 7 (14.6) Neonatal ICU: 19 (39.6)	36 (75) 5 min Apgar < 5: 1 (2.1)	Cord arterial PCO_2: NR
Kugelman 2015[72]	Intervention	Randomized: 32 Analyzed: 25	Age (median): 29.1 weeks (24.5 to 39.0) Sex: NR Weight (median): 1,530g (744 to 2,943g)	Respiratory Distress Syndrome: 19 (76%) Transient tachypnea: 5 (20%) Pneumonia: 1 (4%) Pulmonary hypertension: 2 (8%)	32 (100%)	NR	PCO_2 at study enrolment (median age of 2 days): median 42.3 (24.0 to 55.7

Study	Study Group	Number of Participants	Gestational Age (Mean, SD), % Male Sex; Birth Weight	Respiratory Problems	Intubation	Caesarian Delivery; 5-Minute APGAR	Other
	Control	Randomized: 34 Analyzed: 30	Age: (median) 28.2 weeks (23.5 to 37.9) Sex: NR Weight (median): 1,113g (525 to 3,320g)	Respiratory Distress Syndrome: 27 (90%) Transient tachypnea: 3 (10%) Pneumonia: 0 (0%) Pulmonary hypertension: 3 (10%)	34 (100%)	NR	PCO_2 at study enrolment (median age of 2 days): median 44.3 (34.7 to 72.0)
	Total	Randomized: 66 Analyzed: 55	Age (median): 28.6 weeks (23.5 to 39.0) Sex: NR Weight (median): 1,275g (525 to 3,320g)	Respiratory Distress Syndrome: 46 (70%) Transient tachypnea: 8(12%) Pneumonia: 1 (2%) Pulmonary hypertension: 5 (8%)	66 (100%)	NR	PCO_2 at study enrolment: NR

ICU = intensive care unit; min = minute; mm Hg = millimetres of mercury; NR = not reported; PCO_2 = partial pressure of carbon dioxide; SD = standard deviation

Table 42: Patient Characteristics for the Included Non-randomized Studies for Pediatric Patients in Serious or Critical Condition

Study	Study Group	Number of Participants	Gestational Age (Median, IQR); Birth Weight (Median, IQR)	% Male Sex	Intubation	First PCO_2 Value (Median, IQR)
Hawkes 2015[73]	Intervention	entering: 44 completing: 39	29 + 1 weeks (26 + 5 to 30) 1,225 g (930 to 1540)	60	22.7%	7.45 (5.9 to 8.5)
	Control	entering: 48 completing: 48	29 + 1 weeks (27 to 31) 1,300 g (917 to 1455)	68	31.3%	7.6 (6.3 to 8.8)

IQR = interquartile range; PCO_2 = partial pressure of carbon dioxide.

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

Table 43: Patient Characteristics for the Included Randomized Studies for Adult Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

Study	Study Group	Number of Participants	Age (Mean, SD), % Male Sex, BMI	Comorbid Conditions	Procedure Type	Prescribed Pain Medication	Monitoring Time
Hutchison 2008[32]	Intervention	Entered: 29 Completed: 29	67.6 (SD 9.9) 40% 34.2 (SD 5.2)	Sleep apnea: 0%	Total knee replacement: 17 (59) Bilateral TKR: 5 (17) TKR with bone biopsy: 1 (4) Hip replacement: 6 (21) Shoulder repair: 0 (0)	Dose expressed as parenteral morphine equivalent: 1. Day of surgery: 33.9 (SD 17.9) 2. Post-operative day 1: 26.9 (SD 21)	NR
	Control	Entered: 25 Completed: 25	63.5 (SD 10.7) 24% 34.5 (SD 6.6)	Sleep apnea: 0%	Total knee replacement: 14 (56) Bilateral TKR: 14 (56) TKR with bone biopsy: 2 (8) Hip replacement: 5 (20) Shoulder repair: 2 (8)	Dose expressed as parenteral morphine equivalent: 1. Day of surgery: 41.9 (SD 27.3) 2. Post-operative day 1: 28.1 (SD 21)	NR
	Total	Entered: 54 Completed: 54	Age: NR 31% BMI: NR	Sleep apnea: 0%	Bilateral TKR: 31 (57) TKR with bone biopsy: 19 (35) Hip replacement: 11 (20) Shoulder repair: 2 (4)	NR	NR

BMI = body mass index; NR = not reported; SD = standard deviation; TKR = total knee replacement

Table 44: Patient Characteristics for the Included Non-randomized Studies for Adult Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

Study	Study Group	Number of Participants	Age (Mean, SD), % Male Sex	Comorbid Conditions	Procedure Type	Prescribed Pain Medication	Monitoring Time
Ramsay 2013[74]	Total	Entered: 33 Completed: 33	45 (SD 14) 27% 41 (SD 13)	Sleep apnea: 12 (40) Unknown presence of sleep apnea in 3 patients	Laparoscopic gastric bypass: 11(33) Laparoscopic gastric sleeve: 5 (15) Laparoscopic cholecystectomy: 5 (15) Herniorrhaphy: 2 (6) Cystoscopy and ureteroscopy: 2 (6) Other: 8 (24)	Prescribed PCA: 15 (45) Prescribed narcotics as needed: 30 (97)	112 SD 71 (19.8 to 258.8)

PCA = patient-controlled analgesia; SD = standard deviation.

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Sleep Apnea or Receiving High Doses Of Opioids in Post-Operative Care

No data available.

APPENDIX 10: Detailed Tables for Risk of Bias Assessment

Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

Table 45: Critical Appraisal of RCTs for Adult Patients Undergoing Procedural Sedation

Study	Strengths	Limitations
Adult RCTs		
Klare 2016[51]	Selection bias • Randomization based on a computer-generated sequence with a pre-specified block size. Attrition bias • Analyses were completed for the ITT and PP populations; in tables for patient characteristics, the authors indicated where missing data occurred. Reporting bias No evidence of selective reporting based on the clincialtrials.gov record.	Selection bias • Unclear if study authors used opaque envelopes or an equivalent method to ensure adequate allocation concealment. Performance bias • Patients, endoscopy staff, and physicians were not blind to patient allocation. Detection bias • Independent observers who monitored the patients during the study were not blind to patient allocation. Other biases • Manufacturer supplied the capnography device. • 3 study authors received material support for research purposes from the capnography device manufacturer.
van Loon 2014[61]	**Selection bias** • Method of randomization was described (stratified block randomization by physician). **Attrition bias** • 415/427 (97.2%) of patients were included in the final analysis.	**Selection bias** • Unclear if there was adequate allocation concealment. **Performance bias** • Patients and treatment team were not blinded to patient allocation. **Detection bias** • Unclear if outcome assessors were blind to treatment group. **Reporting bias** • Differences in outcomes indicated in clinicaltrials.gov and those reported in the publication (SpO_2 set at < 90% in clinicaltrials.gov, whereas the publication reports SpO_2 < 91%)
Friederich-Rust 2014[20]	**Selection bias** • Method of randomization was described (stratified block randomization by ASA class, sedation type, procedure type, and study centre) • Endoscopy team was unable to influence the randomization process. **Reporting bias** • Primary outcome reported in clinicatrials.gov is in line with that reported in the publication. **Attrition bias** • 533/539 (98.9%) of patients were included in the final analysis.	**Selection bias** • Baseline imbalance in age between the 2 groups. **Performance bias** • Patients and treatment team were not blinded to patient allocation. **Detection bias** • Unclear who was assessing outcomes. **Other biases** • Baseline imbalance in age between the intervention and control groups.

Study	Strengths	Limitations
	Other strengths • Baseline imbalance in age between the intervention and control groups was adjusted for in the analysis.	
Slagelse 2013[48]	**Selection bias** • Method of randomization was described. • Nurses were blinded for treatment allocation. **Reporting bias** • Primary outcome reported in clinicatrials.gov is in line with that reported in the publication. **Attrition bias** • Patients were excluded if they had missing data. **Other strengths** • Followed eligibility criteria for patients undergoing NAPS (increased generalizability of findings to those patients undergoing NAPS)	**Performance bias** • Nurses were not blinded once the study began. **Detection bias** • Outcome assessors and study investigator were not blinded to treatment allocation during the study. **Reporting bias** • Some of the primary outcome measures stated in the published paper were stated as secondary outcome measures in the clinicaltrials.gov record. **Other biases** • Manufacturer supplied the capnography device.
Beitz 2012[38]	Selection bias • Method of randomization was described. • Endoscopy team was not involved in the randomization. Attrition bias • Analyses were completed for the ITT (though not including 3 patients who withdrew consent after randomization) and PP populations; reasons for patients lost to follow-up were documented. Reporting bias • Primary outcome measure stated in the published paper was the same as what was reported in the clincialtrials.gov record (NCT01072487). Other strengths • Baseline imbalances between treatment groups for history of lung disease and oxygen saturation were adjusted for in the analysis.	Performance bias • Patients and treatment team were not blinded to patient allocation. Detection bias • Outcome assessors were not blind to patient allocation. Other biases • Baseline imbalances between treatment groups for history of lung disease and oxygen saturation. • Manufacturer supplied the capnography device.
Deitch 2010[19]	Selection bias • Method of randomization was described. • Study personnel and treatment team were not involved in the randomization. Detection bias • Before blinding was broken, 3 investigators evaluated the data to assess for the presence or absence of hypoxia and respiratory depression. Attrition bias • Patients were excluded if there was > 35% data loss.	Performance bias • Patients and treatment team were not blinded to patient allocation. Reporting bias • No protocol or clinicaltrials.gov record was found so the presence of reporting bias is unknown. Other biases • Manufacturer supplied the capnography device. Other limitations • Not as many study participants were recruited as anticipated.
Qadeer 2009[54]	Selection bias • Randomization was performed by the institutions biostatistics department. • Concealed envelopes; assessors were not part of the randomization process.	Detection bias • Primary outcome assessors (for hypoxemia) were not blind to patient allocation. Other biases • Manufacturer supplied the capnography device.

Study	Strengths	Limitations
	Performance bias • The endoscopy team was not aware of the capnography readings for either group of patients (the signal of capnography abnormalities was signalled by an independent investigator). Attrition bias • 93.9% of patients were included in the efficacy analysis in both arms; reasons for exclusion were described. Reporting bias • No evidence of selective reporting based on the clinicaltrials.gov record.	

ASA = American Society of Anesthesiologists; ITT = intention-to-treat; NAPS = nurse-administered propofol sedation; PP = per-protocol; RCT = randomized controlled trial; SpO_2 = arterial oxygen saturation measured by pulse oximetry.

Table 46: Critical Appraisal of Non-RCTs for Adult Patients Undergoing Procedural Sedation

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Adult prospective cohort studies			
Barnett 2016[52]	Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcome assessor was not blind to any patient exposure. Authors mentioned that a lack of blinding had the potential to influence the PROSAS assessment. • All patients in the intervention group were continuously monitored with capnography.	Selection bias • Evidence of differences in baseline characteristics between the groups on factors that may influence the outcome. • No indication of the number of patients approached who did not consent. Detection bias • Unclear if the oxygen saturation outcomes was: 1. SpO_2 < 90% **AND** requiring an intervention or if the outcome was: 2. SpO_2 < 90% **OR** requiring an intervention (without a change in SpO_2). Attrition bias • Unclear if there was any missing data or if any patients were lost to follow-up. Detection bias • Outcome assessor was not blind to any patient exposure.	**How well did the study minimize bias?** Low Quality (0) **Clear evidence of association between exposure and outcome?** Cannot say (effect estimates are not provided for the multivariate analysis, there are some imbalances between the intervention and control groups, and there were reported changes in practice over time between the pre-$ETCO_2$ group and $ETCO_2$ group. It is uncertain if there were other changes in practice that were not reported by study authors.) **Results applicable to the patient group targeted?** Yes (patients undergoing colonoscopy with moderate sedation) **Author conclusions:** The authors conclude that adding capnography to standard monitoring did not improve safety or patient satisfaction for patients undergoing colonoscopy under moderate sedation. The use of capnography required additional cost. The authors also suggest that future research should assess the value of capnography for specific subpopulations that may benefit from the use of capnography.
Tanaka 2014[56]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined. • All patients were continuously monitored with capnography. Attrition bias • 5% of patients did not complete the study. Other strengths • Confidence intervals were provided.	Selection bias • No indication of the number of patients approached who did not consent. Detection bias • Outcome assessor was not blind to any patient exposure. No mention of lack of blinding potentially influencing outcome assessment. • It is unclear if the study investigators were trained in identifying the outcome measures that were used. Reporting bias • No protocol available.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No (considered a pilot study; results do not necessarily capture all true respiratory pauses because the retrospective review of data only looks at a minute before and a minute after the event that was detected by one of the interventions). **Results applicable to the patient group targeted?** Yes **Author conclusions:** Apnea and excessive sedation occur in patients undergoing monitored anesthetic care; acoustic monitoring provided the highest probability of detecting respiratory pause and the lowest probability of missing a respiratory pause. Acoustic monitoring may be

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
		Other biases • Manufacturer supplied the rainbow acoustic monitor. Other limitations • Potential confounders were mentioned in the limitations section but it is unclear if they were considered for the analysis.	the most effective option (versus capnography and clinical observation) for monitoring ventilation during procedural sedation.
Schlag 2013[59]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined; references for the definition of the primary outcome were provided. • All patients were continuously monitored with capnography. • All study data and observations were recorded by an investigator who was not involved in patient care. Attrition bias • No patients were lost to follow-up. Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	Selection bias • No indication of the number of patients approached who did not consent. Detection bias • Outcome assessor was not blind to any patient exposure. • It is unclear if the study investigators were trained in identifying the outcome measures that were used. Reporting bias • No protocol available. Other biases • Manufacturer supplied the capnography device.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No (small sample size, not intended to be an interventional study) **Results applicable to the patient group targeted?** Yes (for adult patients undergoing procedural sedation for percutaneous transhepatic cholangiodrainage). **Author conclusions:** Authors found that capnography was more effective for capturing episodes of apnea, and predicting episodes of oxygen desaturation compared with standard monitoring and observation in patients undergoing procedural sedation for percutaneous transhepatic cholangiodrainage. Authors recognized the limitations of study design, limited sample size.
Kusunoki 2012[60]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined.	Selection bias • No indication of the number of patients approached who did not consent. Detection bias • Outcome assessor was not blind to any patient exposure. No mention of lack of blinding potentially influencing outcome assessment.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** Cannot say (results are suggestive of an association between $ETCO_2$ and the ability to detect respiratory changes; however, due to the few number of events, the association is uncertain.) **Results applicable to the patient group targeted?** Yes

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
	• All patients were continuously monitored with capnography. Other biases • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	• No discussion of the validity of SpO_2 for detecting hypoxia or references for its definition. Attrition bias • Unclear if there was any missing data or if any patients were lost to follow-up. Reporting bias • No protocol available.	**Author conclusions:** Authors concluded that $ETCO_2$ values correlated with $PtCO_2$ values, and respiratory monitoring methods allowed earlier detection of hypoxia for patients under conscious sedation (when compared with transcutaneous methods). **Other notes:** There were a small number of events and $PtCO_2$ monitoring did not identify any events so it is unclear if these results would be confirmed in a larger trial.
De Oliveira 2010[53]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. • 98% (40/41) patients who were approached for enrolment agreed to participate in the study. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined; rationale provided for the definition of hypoventilation. • All patients were continuously monitored with capnography. Attrition bias • One patient had missing data that was excluded from the analysis. Reporting bias • No indication of differences in outcomes between the published article and the clincialtrials.gov record (NCT00954733) Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	Detection bias • Outcome assessor was not blind to any patient exposure. No mention of lack of blinding potentially influencing outcome assessment.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** Yes (the results were consistent with other studies in the area. Anesthesia staff was blinded to transcutaneous capnography) **Results applicable to the patient group targeted?** Yes (very specific target population: women undergoing hysteroscopy) **Author conclusions:** Authors concluded that $TcCO_2$ was more sensitive than $ETCO_2$ and may provide a better assessment of hypoventilation for women undergoing deep sedation. Very specific patient population and women were otherwise healthy.
Cacho 2010[62]	Selection bias • Only one group of patients was selected for inclusion — no differences between	Selection bias • No indication of the number of patients approached who did not	**How well did the study minimize bias?** Low Quality (0)

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
	groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined; references were provided for $ETCO_2$ and SpO_2. • All patients were continuously monitored with capnography. Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	consent. Detection bias • Outcome assessor was not blind to any patient exposure. No mention of lack of blinding potentially influencing outcome assessment. • It was not stated if the study investigators were trained in the outcome measures used. Attrition bias • No mention of missing data. Reporting bias • No protocol available.	**Clear evidence of association between exposure and outcome?** No (methodology unclear; not clear the actual number of episodes of disordered respiration) **Results applicable to the patient group targeted?** Yes (patients undergoing colonoscopy with sedation) **Author conclusions:** Authors conclude that capnography is a useful compliment to patient monitoring based on visual assessment and pulse oximetry in patients undergoing colonoscopies with sedation. Authors also state that capnography allows for earlier detection of respiratory abnormalities and is more sensitive in detecting these abnormalities.
Deitch 2008[55]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. • Patients were enrolled 24 hours/day, 7 days/week. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. • All patients were monitored with $ETCO_2$ but physicians were blinded to the monitoring data. Detection bias • Outcomes were clearly defined; validated outcome measures were used. • Authors recognize that where blinding was not possible, the outcome assessors having knowledge of patient exposure status could have influenced the outcome. • $ETCO_2$ was recorded at baseline and every 5 minutes until the patient returned to baseline alertness. Attrition bias • No patients were lost to follow-up. Other strengths	Selection bias • No indication of the number of patients approached who did not consent. Detection bias • Outcome assessor was not blind to patient exposure. Reporting bias • No protocol available.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No (the study was not designed to assess the effects of $ETCO_2$ monitoring; the assessment of the use of capnography for identifying patients who may become hypoxic was a secondary objective.) **Results applicable to the patient group targeted?** Yes (patients undergoing procedural sedation with propofol) **Author conclusions:** The authors conclude that the use of capnography allowed for the detection of respiratory depression that was otherwise undetected by the clinical care team. **Other notes:** Although capnography was found to detect a greater number of episodes of respiratory depression, it is uncertain how this would change patient outcomes because the clinicians were blinded to the $ETCO_2$ monitor. It is also noticeable that not all cases of respiratory changes that were detected by capnography led to a hypoxic event.

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
	• All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)		
Deitch 2007[57]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. • Patients were enrolled 24 hours per day, 7 days per week. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. • All patients were monitored with $ETCO_2$ but physicians were blinded to the monitoring data. Detection bias • Outcomes were clearly defined. • Authors recognize that where blinding was not possible, the outcome assessors having knowledge of patient exposure status could have influenced the outcome. • $ETCO_2$ was recorded at baseline and every 5 minutes until the patient returned to baseline alertness. Attrition bias • No patients were lost to follow-up. Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	Selection bias • No indication of the number of patients approached who did not consent. Detection bias • Outcome assessor was not blind to patient exposure. • No references or rationale was provided for outcomes. Reporting bias • No protocol available.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No (the study was not designed to assess the effects of $ETCO_2$ monitoring; the assessment of the use of capnography for identifying patients who may become hypoxic was a secondary objective.) **Results applicable to the patient group targeted?** Yes (patients undergoing procedural sedation and analgesia with midazolam and fentanyl) **Author conclusions:** The authors conclude that the use of capnography allowed for the detection of respiratory depression that was otherwise undetected by the clinical care team. **Other notes:** Although capnography was found to detect a greater number of episodes of respiratory depression, it is uncertain how this would change patient outcomes because the clinicians were blinded to the $ETCO_2$ monitor. It is also noticeable that not all cases of respiratory changes that were detected by capnography led to a hypoxic event.
Burton 2006[58]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. • Patients and treatment team was blinded	Selection bias • Patients were only recruited when the study investigator was present. • No indication of the number of patients approached who did not consent. Detection bias • It was not stated if the study	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** Cannot say (the study was terminated based on an interim safety analysis that $ETCO_2$ predicted respiratory events prior to oxygen saturation monitoring). **Results applicable to the patient group targeted?** Yes **Author conclusions:** The authors conclude that

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
	to monitoring data. Detection bias • Outcomes were clearly defined; definition of $ETCO_2$ change was provided. • Study data and observations were recorded by an investigator who was not involved in patient care. • All patients were continuously monitored with capnography. Attrition bias • No patients were lost to follow-up. Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	investigators were trained in the outcome measures used. Reporting bias • No protocol available.	capnography allowed for the earlier detection of acute respiratory events compared with changes in pulse oximetry, and events detected by clinical observation of hypoventilation and apnea. The authors also recognize that the early recognition of acute respiratory events by $ETCO_2$ does not necessarily translate into a clinically meaningful event, and does not necessarily suggest that a change in clinical management would lead to a clinical improvement in respiratory status of the patient. **Other notes:** The study was terminated early based on the understanding that $ETCO_2$ was detecting respiratory events prior to other forms of monitoring. This is suggestive of an effect, but the study was not completed.
Soto 2005[50]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. • Patients and treatment team was blinded to monitoring data. Detection bias • Outcomes were clearly defined. • All patients were continuously monitored with capnography. Attrition bias • No patients were lost to follow-up. Other strengths • All patients were monitored with capnography and standard monitoring (i.e., inter-individual assessment so confounding is not applicable)	Detection bias • It was unclear who was assessing the capnography display Reporting bias • No protocol available.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** Cannot say (the study was not designed to assess the effects of $ETCO_2$ monitoring; some of the study methodology was unclear.) **Results applicable to the patient group targeted?** Yes (patients undergoing monitored anesthesia care) **Author conclusions:** The study was not designed to assess the effectiveness of capnography, so the authors make no conclusions regarding its effectiveness. The authors conclude that apnea is more likely with lower levels of patient consciousness. **Other notes:** Patients' level of sedation is not clear. The data indicates that the majority of patients were at minimal or moderate sedation, but this was not explicitly stated. Some details of the methodology of the study are unclear, such as how the > 60 seconds of apnea were signalled to the treating team, and who was responsible for monitoring the capnography device since the treating team was blind to its' display.

$ETCO_2$ = end-tidal carbon dioxide; PROSAS = Procedural Sedation Assessment Survey; $PtCO_2$ = transcutaneous carbon dioxide; RCTs = randomized controlled trials; SpO_2 = arterial oxygen saturation measured by pulse oximetry; $TcCO_2$ = transcutaneous carbon dioxide.

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Table 47: Critical Appraisal of RCTs for Pediatric Patients Undergoing Procedural Sedation

Study	Strengths	Limitations
Pediatric Randomized Studies		
Langhan 2015[68]	**Selection bias** • Randomization performed by a statistician in blocks of 6. • Patients were allocated to treatment arms using sealed, opaque envelopes. **Reporting bias** • No indication of selective outcome reporting.	**Performance bias** • Patients and treatment team were not blinded to patient allocation. **Detection bias** • Outcome assessors were not blind to patient allocation. **Attrition bias** • Incomplete outcome data were not addressed. **Other limitations** • Study may have been underpowered to detect hypoxemia; study not powered to detect severe adverse events.
Lightdale 2006[65]	**Selection bias** • Randomization was based on permuted blocks of 2, 4, 6, 8 and was stratified by procedure type. • Randomization was performed by independent observers. **Performance bias** • Patients and treatment team were blinded to patient allocation. **Attrition bias** • No patients were lost to follow-up.	**Reporting bias** • Unclear if there was selective outcome reporting. **Detection bias** • The primary outcome, oxygen desaturation was recorded by independent observers who were not blinded to patient randomization arms. **Other biases** • Manufacturer supplied the capnography filter lines and the capnography device. **Other limitations** • Authors report that the pulse oximetry results may have been different had newer technologies been used.

$ETCO_2$ = end-tidal carbon dioxide; RCT = randomized controlled trial.

Table 48: Critical Appraisal of Non-RCTs for Pediatric Patients Undergoing Procedural Sedation

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Pediatric prospective cohort studies			
Kannikeswaran 2011[67]	Selection bias • Only 1 group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined; references provided for the validity of $ETCO_2$. • The research assistants were trained in $ETCO_2$ monitoring. Attrition bias • No patients were lost to follow-up.	Selection bias • No indication of the number of patients approached who did not consent. • Patients were recruited on the basis of a convenience sample (8 a.m. to 6 p.m.). • Patients were excluded from the study due to $ETCO_2$ device malfunction or nasal cannula dislodgement and removal. Detection bias • Research assistant were aware of all patient monitoring modalities. Reporting bias • Unclear if there was selective outcome reporting. Other biases • Manufacturer supplied the nasal cannulas.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No (uncertain if the visibility of the $ETCO_2$ data to the sedation team influenced outcomes. However, it was stated that physicians "performed interventions for oxygen desaturations and other airway adverse events and not for $ETCO_2$ abnormalities." Twenty percent of subjects did not have baseline $ETCO_2$ values due to intolerance to the nasal cannula. **Results applicable to the patient group targeted?** Yes (very specific target population: children with developmental disabilities undergoing a brain MRI) **Author conclusions:** The authors conclude that the use of capnography allows for early detection of hypoxia and respiratory events in children with developmental disabilities undergoing sedation.
Anderson 2007[66]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were well defined. Attrition bias • Only one group of patients so there is no differential in dropout between an intervention and control group.	Selection bias • Convenience sample of patients (75% of those eligible). Detection bias • Unclear if the research assistants were trained in $ETCO_2$ monitoring. Reporting bias • Unclear if there was selective outcome reporting. Attrition bias • Two patients required open surgical repair; not clear if they were included in the analysis.	**How well did the study minimize bias?** Low Quality 0 **Clear evidence of association between exposure and outcome?** No (limited sample, uncertain methodology — not clear if the sedation team could see the $ETCO_2$ readings) **Results applicable to the patient group targeted?** Yes (children undergoing propofol sedation for orthopedic reduction). **Author conclusions:** The authors concluded that the use of capnography allowed for the earlier detection of apnea compared with clinical observation and pulse oximetry in children undergoing propofol sedation for orthopedic reduction. This allowed for earlier intervention.

$ETCO_2$ = end-tidal carbon dioxide; MRI = magnetic resonance imaging; RCTs = randomized controlled trials.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

Table 49: Critical Appraisal of Non-RCTs for Adult Patients Undergoing CPR

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Adult Prospective Cohort Studies			
Chen 2015[1]	Selection bias • Patients in the intervention and control group were selected from the same cohort of patients. A table of patient characteristics was provided to compare factors in the intervention and control groups. Performance bias • The study was a retrospective chart review where patients were classified as having received $ETCO_2$ or not so it is unlikely that there is a systematic difference in the treatment provided between the intervention and control group. Detection bias • The authors recognized the possibility that a measurement of exposure status (i.e., the use of $ETCO_2$) may not have been recorded and billed in all cases.	Selection bias • A comparison of baseline characteristics between the $ETCO_2$ and no-$ETCO_2$ group suggest that the propensity score matching may not have been ideal (for example, 53% male in the $ETCO_2$ group versus 63% male in the no-$ETCO_2$ group). • Patients with an out-of-hospital cardiac arrest were selected based on ICD codes for ventricular fibrillation, cardiac arrest, and sudden death. The authors do not present a comparison of the number of cases for each indication (by ICD code) between cases and controls. Detection bias • Hospital admission was used as a surrogate for ROSC. Survival to hospital discharge was known only if it was cited in the clinical records. There was no discussion of the validity of this approach. • Unclear if exposure status was known prior to the assessment of outcomes by the personnel responsible for data extraction.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** No. Study control group was based on propensity score matching with the intervention group for a number of factors (age, sex, date, urbanization level, health care institutes, SES, CPR duration, and attempted defibrillation); however, the authors do not present data on the number of patients who fell within each ICD code for cases and controls. It is possible that there were differences in the proportion of patients in each ICD code between cases and controls, and therefore a systematic difference between the rate of exposure and outcome between the two groups. The authors adjust for clinically relevant variables, perform a sensitivity analysis for unmeasured confounding, and perform a 1:4 ratio for matching to assess the consistency of results compared with the main analysis (1:20 match). The number of patients exposed to $ETCO_2$ was low (n = 53 in the 1:20 match) **Results applicable to the patient group targeted?** Yes (out-of-hospital cardiac events) **Author conclusions:** The authors suggest that patients who are monitored with $ETCO_2$ have a greater potential for attaining sustained return of spontaneous circulation. There was no statistically significant difference in the percentage of patients who survive until hospital discharge.

CPR = cardiopulmonary resuscitation; CWI = chest wall impedance**;** $ETCO_2$ = end-tidal carbon dioxide; ICD = international classification of diseases; RCTs = randomized controlled trials; ROSC = return of spontaneous circulation; SES = socioeconomic status.

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No data available.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition

Table 50: Critical Appraisal of Non-RCTs for Adult Patients in Serious or Critical Condition

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Adult Prospective Cohort Studies			
Bhat 2014[69]	Performance bias • Retrospective analysis — no outcome at enrolment. Detection bias • Outcomes were clearly defined and valid. • The research assistants were blinded to the hypothesis of the study when extracting data.	Selection bias • Retrospective study that only included patients who had complete data available. • No details of patient characteristics provided.	**How well did the study minimize bias?** Acceptable (+) **Clear evidence of association between exposure and outcome?** Unclear (retrospective study, very few patients were monitored with capnography) **Results applicable to the patient group targeted?** Yes (very specific patient population) **Author conclusions:** No conclusions were made that were specific to $ETCO_2$ monitoring. Generally, authors concluded that post-intubation interventions were not associated with ventilator-associated pneumonia, ICU length of stay or number of ventilator days. Results are not generalizable to those with a DNR order.
Silvestri 2005[70]	Selection bias • Respiratory therapy log was used to capture all intubated patients. • All patients arriving to the ED with ETT in place were included. Detection bias • Primary outcome (correct placement of the ETT) was measured at enrolment, prior to knowledge of patient exposure status. • Outcomes were clearly defined. Attrition bias • No patients were lost to follow-up.	Recall bias • Use of capnography (exposure status) in the field was based on self-report by the treatment team which is subject to recall bias. Detection bias • Exposure status was measured retrospectively after the primary outcome was assessed. Other biases • One study author was a consultant for the capnography manufacturer. Other limitations • No control for confounding variables such as patient and provider factors.	**How well did the study minimize bias?** Low Quality (0) **Clear evidence of association between exposure and outcome?** No (small sample size, limited control for confounders, out-of-hospital $ETCO_2$ use was dependent on paramedic recall and was determined after assessment of the primary outcome) **Results applicable to the patient group targeted?** Yes (patients requiring out-of-hospital ETT placement) **Author conclusions:** When continuous $ETCO_2$ monitoring was used by EMS there was no incidence of misplaced ETT that was not identified whereas unrecognized misplaced ETT occurred 23% of the time when $ETCO_2$ was not used. The association is likely "true" as $ETCO_2$ provides continuous monitoring and the alternative in the EMS setting is clinical observation, which is not continuous.

DNR = do not resuscitate; ED = emergency department; EMS = emergency medical service; $ETCO_2$ = end-tidal carbon dioxide; ETT = endotracheal tube; ICU = intensive care unit; RCTs = randomized controlled trials.

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Table 51: Critical Appraisal of RCTs for Pediatric Patients in Serious or Critical Condition

Study	Strengths	Limitations
Pediatric randomized studies		
Kong 2013[71]	**Selection bias** • Randomization performed in blocks of 4 according to gestational age. • Patients were allocated to treatment arms using opaque envelopes; treatment team was not involved in the randomization process. **Attrition bias** • 96% (48/50) of patients had complete outcome data; reasons for attrition were reported.	**Selection bias** • The most critically ill infants were not included. **Performance bias** • Patients and treatment team were not blind to patient allocation. **Detection bias** • Unclear who was responsible for obtaining outcome data and if they were blind to patient allocation. • Arbitrary threshold of 40 to 60 mm Hg was set for the desired PCO_2 range — no references were provided. **Reporting bias** • $ETCO_2$ values were not reported in the study but were stated to be measured. **Other limitations** • Small sample size
Kugelman 2015[72]	**Attrition bias** • Reasons for missing data were reported (technical problems).	**Selection bias** • Unclear how the pre-prepared list for randomization was generated; method of allocation not stated. **Performance bias** • Patients and treatment team were not blind to patient allocation. **Detection bias** • Unclear who was responsible for measuring the primary outcome PCO_2 and other measures. • Unclear if (but seems likely that) the treatment team was able to see the capnograph waveform display during treatment in the control group. Potential bias towards no difference between the groups. **Attrition bias** • Imbalance in the number of patients excluded from the analysis between groups (6/25, 24% in the intervention group; 2/30, 7% in the control group). **Reporting bias** • Results for the primary outcome are not reported. **Other biases** • Manufacturer supplied the capnography device and sampling lines. • One of the study authors was employed by the manufacturer **Other limitations** • Inadequate reporting of methods of statistical analysis.

$ETCO_2$ = end-tidal carbon dioxide; mm Hg = millimetres of mercury; PCO_2 = partial pressure of carbon dioxide; RCT = randomized controlled trial.

Table 52: Critical Appraisal of Non-RCTs for Pediatric Patients in Serious or Critical Condition

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Pediatric prospective cohort studies			
Hawkes 2015[73]	Selection bias • Historical control group was identified from a study with the same inclusion/exclusion criteria and there was no change in resuscitation training or practice between the two groups. Performance bias • All infants were assessed immediately following birth — no outcome at enrolment. Attrition bias • 11% of patients were lost to follow-up; reasons for attrition were provided.	Selection bias • Convenience sample. • Unclear how many patients in the historical cohort were asked to participate and agreed to participate. Attrition bias • No details regarding patients who were lost to follow-up in the historical control group. Detection bias • Primary and secondary outcomes were not explicitly stated; definitions of outcomes were not clearly described and target ranges were not referenced. • Researchers and medical team were aware that $ETCO_2$ was being monitored; no recognition of the potential impacts of no blinding.	**How well did the study minimize bias?** Low Quality (0) **Clear evidence of association between exposure and outcome?** Unclear (assessment of the effectiveness of $ETCO_2$ monitoring was not the primary objective of the study. No explanation of the potential effects the $ETCO_2$ monitor had on the interventions carried out by the medical team. Unknown what standard monitoring equipment was available to clinicians for monitoring patients in the historical control group.) **Results applicable to the patient group targeted?** Yes (preterm infants) **Author conclusions:** The primary aim of the study was to assess $ETCO_2$ measures within the first 10 minutes of an infant's life. In addition to this aim, the authors hypothesized that infants who had $ETCO_2$ monitoring would be more likely to have PCO_2 levels within an acceptable range. There was no statistically significant difference in the percentage of infants having PCO_2 values within the target range between the two groups. The authors note the importance of human error in the use of these devices, and suggest that future studies look at the effects of $ETCO_2$ monitoring on other measures such as SpO_2 and heart rate. **Other notes:** Study based on a small sample size with little known about potential confounders.

$ETCO_2$ = end-tidal carbon dioxide; PCO_2 = partial pressure of carbon dioxide; RCTs = randomized controlled trials; SpO_2 = arterial oxygen saturation measured by pulse oximetry

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

Table 53: Critical Appraisal of RCTs for Adult Patients Being Monitored in Post-operative Care

Study	Strengths	Limitations
Adult randomized studies		
Hutchison 2008[32]		**Selection bias** • Method of randomization not described. **Performance bias** • Patients and treatment team were not blind to patient allocation. **Detection bias** • Outcome assessors were not blind to patient allocation. **Attrition bias** • Missing data not addressed. **Other biases** • Manufacturer supplied the capnography device. • Manufacturer provided an honorarium to one of the study authors for speaking at a convention. **Other limitations** • All events were detected by respiratory rate changes or apnea detection, not by pulse oximetry or capnography — suggests that there may be something else besides the devices that are detecting events differentially between the groups. • Clinicaltrials.gov record suggests that the primary objective of the study was to look at the value of capnography for detecting undiagnosed obstructive sleep apnea.

RCT = randomized controlled trial.

Table 54: Critical Appraisal of Non-RCTs for Adult Patients Being Monitored in Post-Operative Care

Study	Strengths	Limitations	Overall Assessment and Author Conclusions
Adult prospective cohort studies			
Ramsay 2013[74]	Selection bias • Only one group of patients was selected for inclusion — no differences between groups. Performance bias • Patients were recruited prior to the start of the procedure — no outcome at enrolment. Detection bias • Outcomes were clearly defined. • The reference comparison (combination of acoustic and capnography data) was evaluated by trained technician and confirmed by a second technician.	Selection bias • Convenience sample of patients. • Unclear how many patients in the historical cohort were asked to participate and agreed to participate Attrition bias • Missing data not addressed. Detection bias • Unclear if technicians were blind to patient allocation or study hypothesis. Other biases • Potential confounders not addressed. • Funding for the research personnel who collected the study data and provided the equipment was provided by the device manufacturer. • The authors of the study received manufacturer funding. • One study author was employed by the manufacturer.	**How well did the study minimize bias?** Low Quality (0) **Clear evidence of association between exposure and outcome?** Yes (both devices reliably detected respiratory pauses) **Results applicable to the patient group targeted?** Yes **Author conclusions:** Authors conclude that acoustic monitoring is more reliable than $ETCO_2$ and recognized that the clinical significance of this increased precision is unknown. **Other notes:** This study included a small sample with a small number of ventilatory pauses and did not analyze the effects of monitoring separately for patients diagnosed with obstructive sleep apnea at baseline. It is unclear whether this finding would be replicable in a larger sample.

$ETCO_2$ = end-tidal carbon dioxide; RCT = randomized controlled trial.

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-operative Care

No data available.

APPENDIX 11: Detailed Outcome Results — Clinical Review

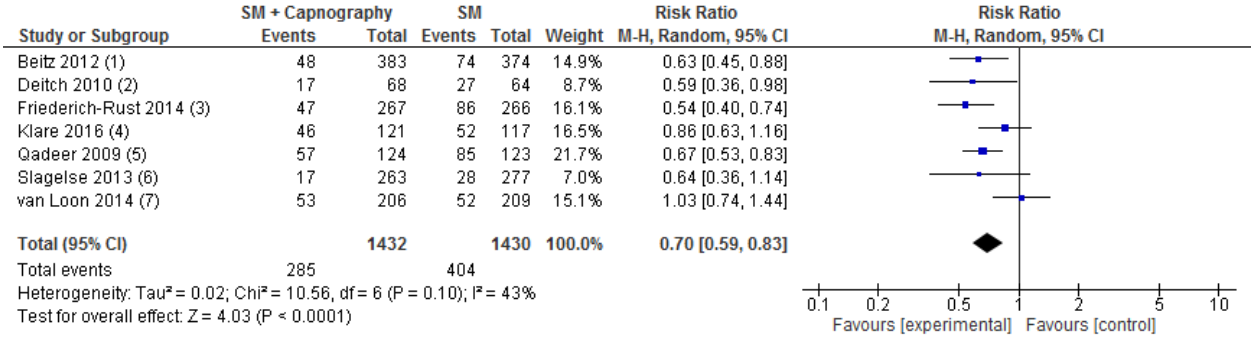
Research Question 1: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Procedural Sedation

Table 55: Detailed Outcome Data for the Pooled Analysis for rhe Primary Outcome: Hypoxemia and Severe Hypoxemia

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
			Standard monitoring + capnography visible			Standard monitoring or standard monitoring + capnography not visible			
			n	N	%	n	N	%	
Klare 2016[51]	SpO_2 < 90% (hypoxemia)[b]	Primary	46	121	38.0	52	117	44.4	0.314
Klare 2016[51]	SpO_2 < 85% (hypoxemia)[c]	Secondary	27	121	22.3	31	117	26.5	0.453
Van Loon 2014[61]	SpO_2 < 91% (hypoxemia)[b]	Primary	53	206	25.7	52	209	24.9	0.843
Van Loon 2014[61]	SpO_2 < 81% (profound hypoxemia)[c]	Secondary	7	206	3.4	6	209	2.9	0.76
Friederich-Rust 2014[20]	SpO_2 < 90% for ≥ 15 sec (hypoxemia)[b]	Primary	47	267	18	86	266	32	< 0.001
Friederich-Rust 2014[20]	SpO_2 < 85% (severe hypoxemia)[c]	Secondary	15	267	6	22	266	8	0.24
Slagelse 2013[48]	SpO_2 < 92% (hypoxic events)[b]	Primary	17	263	6.5	28	277	10.1	0.6
Slagelse 2013[48]	SpO_2 < 88% (level of hypoxia)[c]	Primary	33	263	13.0	32	277	11.6	0.56
Beitz 2012[38]	SpO_2 < 90% (hypoxemia)[b]	Secondary	48	383	12.5	74	374	19.8	0.008
Beitz 2012[38]	SpO_2 < 85% (severe hypoxemia)[c]	Secondary	14	383	3.7	29	374	7.8	0.018
Qadeer 2009[54]	SpO_2 < 90% for ≥ 15 sec (hypoxemia)[b]	Primary	57	124	46	85	123	69.1	< 0.001
Qadeer 2009[54]	SpO_2 < 85% (severe hypoxemia)[c]	Secondary	19	124	15.3	38	123	30.9	0.004
Deitch 2010[19]	SpO_2 < 93% for ≥ 15 seconds (hypoxia)[b]	NR	17	68	25	27	64	42	NR[d]

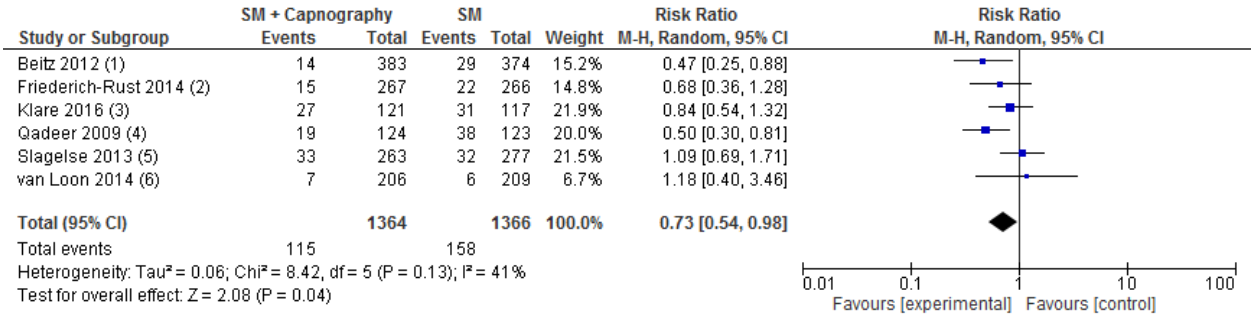
CI = confidence interval; NR = not reported; SpO_2 = arterial oxygen saturation measured by pulse oximetry.
[a] Study reported definition of outcome.
[b] Included in the pooled analysis for hypoxemia.
[c] Included in the pooled analysis for severe hypoxemia
[d] Study reported an effect size (difference 1% [95% CI, 16 to 17]).[19]

Figure 5: Random Effects Meta-Analysis for Hypoxemia, Adults Undergoing Procedural Sedation With Capnography and Standard Monitoring Versus Standard Monitoring Alone



Footnotes
(1) Hypoxemia defined as SpO2 < 90%
(2) Hypoxemia defined as SpO2 < 93% for at least 15 seconds
(3) Hypoxemia defined as SpO2 < 90% for at least 15 seconds
(4) Hypoxemia defined as SpO2 < 90%
(5) Hypoxemia defined as SpO2 < 90% for at least 15 seconds
(6) Hypoxemia defined as SpO2 < 92%
(7) Hypoxemia defined as SpO2 < 91%

Figure 6: Random Effects Meta-Analysis for Severe Hypoxemia, Adults Undergoing Procedural Sedation With Capnography and Standard Monitoring Versus Standard Monitoring Alone



Footnotes
(1) Severe hypoxemia defined as SpO2 < 85%
(2) Severe hypoxemia defined as SpO2 < 85%
(3) Severe hypoxemia defined as SpO2 <= 85%
(4) Severe hypoxemia defined as SpO2 < 85%
(5) Level of hypoxia defined as SpO2 < 88%
(6) Profound hypoxemia defined as SpO2 < 81%

Table 56: All Reported SpO_2 Measures

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
Randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
van Loon 2014[61]	SpO_2 < 91% for ≥ 60 seconds (prolonged hypoxemia)	Secondary	8	206	3.9	3	209	1.4	0.12
Slagelse 2013[48]	SpO_2 < 92 to 90% (level of hypoxia)	Primary	36	263	13.7	55	277	19.9	0.1
	SpO_2 < 90 to 88% (level of hypoxia)	Primary	16	263	6.1	22	277	7.9	0.57
			Standard monitoring + capnography visible			**Standard monitoring + capnography not visible**			
			n	**N**	**%**	**n**	**N**	**%**	
Klare 2016[51]	SpO_2 < 80% (hypoxemia)	Not stated	15	121	12.4	15	117	12.8	0.922
Beitz 2012[38]	SpO_2 decrease > 5% from baseline or SpO_2 < 90% (oxygen desaturation)	Primary	149	383	38.9	199	374	53.2	< 0.001
Non-randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Barnett 2016[52]	O_2 saturation < 90% or requiring intervention	Not stated	NR	501	5	NR	465	2.4	0.04[b]
			Capnography data			**Standard monitoring data**			
			All patients received standard monitoring + capnography						
Schlag 2013[59]	SpO_2 < 90% (hypoxemia)[c]	Secondary	3	3	100	1	3	33.3	0.22
	SpO_2 decrease ≥ 5% (oxygen desaturation)[c]	Secondary	8	10	80	2	10	20	0.06

SpO_2 = arterial oxygen saturation measured by pulse oximetry.
[a] Outcome based on study-reported terminology and definition.
[b] Results are unadjusted; no data available for the adjusted analysis to account for the baseline differences in patient characteristics.
[c] Number of episodes predicted by capnography and by standard monitoring (clinically).

Table 57: All Respiratory Events Detected for Each Included Study (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Friederich-Rust 2014[20]	Apnea or bradypnea[a]	Secondary	183	267	69	NR	NR	NR	NR
			Standard monitoring + capnography visible			**Standard monitoring + capnography not visible**			
			n	**N**	**%**	**n**	**N**	**%**	
Beitz 2012[38]	Apnea or altered ventilation[b]	Secondary	217	383	56.7	8	374	2.1	< 0.001
Deitch 2010[19]	Respiratory depression[c]	Not stated	39	68	57	37	64	58	NR[c]
Klare 2016[51]	Apnea[d]	Secondary	78	121	64.5	7	117	6	< 0.001
			Standard monitoring + capnography signal[e]			**Standard monitoring + delayed capnography signal[e]**			
			n	**N**	**%**	**n**	**N**	**%**	
Qadeer 2009[54]	Apnea[f]	Secondary	51	124	41.1	77	123	62.6	< 0.001
	Abnormal ventilation[g]	Secondary	95	124	76.6	101	123	82.1	0.29
Non-randomized studies (adult patients)									
			Capnography data			**Standard monitoring data**			
			All patients received standard monitoring + capnography not visible						
			n	**N**	**%**	**n**	**N**	**%**	
Schlag 2013[59]	Apnea[h]	Secondary	16	20	80	6	20	30	0.001
Cacho 2010[62]	Hypoventilation[i]	Not stated	12[j]	NR	NR	6[j]	NR	NR	NR
	Apnea[k]	Not stated	17[j]	NR	NR	5[j]	NR	NR	NR

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Deitch 2008[55] Supplemental O_2 group	Respiratory Depression[l]	Not stated	23	30	77	11	30	37	NR
Deitch 2008[55] Room air group			13	22	59	13	22	59	NR
Deitch 2007[57] Supplemental O_2 group	Respiratory depression[l]	Not stated	19	20	95	3	20	15	NR
Deitch 2007[57] Room air group			16	19	84	5	19	26	NR
Burton 2006[58]	Acute respiratory events (based on 20 events detected from 60 encounters with 59 patients)[m]	Not stated	17[n]	20	85	20	20	100	NR
Soto 2005[50]	Apnea[o]	Not stated	49	99	49	0	99	0	NR

NR = not reported; $ETCO_2$ = end-tidal carbon dioxide; O_2 = oxygen.
[a] Apnea was defined by capnographic criteria ($ETCO_2$ = 0 for > 10 seconds) or Bradypnea (< 8 breaths/minute).[20]
[b] Apnea was defined by capnographic criteria only (absence of $ETCO_2$ or altered ventilation [reduction of $ETCO_2$ of more than half of baseline]).[38]
[c] Respiratory depression was defined by capnographic criteria only ($ETCO_2$ > 50 mm Hg, $ETCO_2$ change from baseline ≥ 10%, waveform loss ≥ 15 seconds); Difference between groups: 1% (95% CI, –16 to 17).[19]
[d] Apnea was defined by capnographic criteria ($ETCO_2$ = 0 for ≥ 15 seconds)
[e] The treatment team in the intervention group was signalled by an independent observer of abnormalities within 5 to 10 seconds of appearance on the capnography monitor (included a flat waveform for > 5 seconds, > 75% reduction in waveform amplitude compared with baseline, or respiratory rate of < 8 breaths/minute). The treatment team of the control group was signalled for prolonged apnea (> 30 seconds).[54]
[f] Apnea was defined by capnographic criteria (flat capnographic waveform ≥ 15 seconds) or absence of respiratory activity.[54]
[g] Abnormal ventilation was defined by capnographic criteria only (flat capnographic waveform for ≥ 5 seconds and < 15 seconds or > 75% reduction in waveform amplitude compared with baseline for ≥ 5 seconds).[54]
[h] Apnea was defined by capnographic criteria (decrease of exhaled partial pressure of CO_2 < 8 mm Hg for ≥ 15 seconds) and clinically as the cessation of breathing as observed by the physician.[59]
[i] Hypoventilation was defined by capnography criteria only ($ETCO_2$ ≥ 25% higher than baseline).[62]
[j] Number of respiratory abnormalities events detected by capnography (intervention) compared with pulse oximetry (control).[62]
[k] Apnea was defined as the cessation of breathing for ≥ 30 seconds.[62]
[l] Defined by capnographic criteria ($ETCO_2$ > 50 mm Hg, $ETCO_2$ > 10 mm Hg change from baseline, loss of waveform), SpO_2 (< 93%) or by clinical detection (verbal indication from treatment team that the patient was experiencing respiratory depression, or the treating team provided an intervention to assist breathing).[55]
[m] Acute respiratory event defined as SpO_2 ≤ 92% and clinical interventions (increase supplemental oxygen, ventilation assistance, airway realignment, verbal or physical stimulation, use of reversal drugs).[58]
[n] In 14 of the 17 patients with acute respiratory events, $ETCO_2$ abnormalities were detected before changes in pulse oximetry and clinical observation.[58]
[o] Apnea was defined as apnea for > 60 seconds; for the 20 patients who experienced oxygen saturation < 90%, apnea was detected by capnography in 11 of the 20 patients, and for 6 patients, hypoxemia occurred before the detection of apnea by capnography (the remaining three patients experienced hypoxemia but did not experience a detected apnea event).[50]

Table 58: All Respiratory Events Detected for Each Included Study (Capnography Versus Standard Monitoring and Versus Rainbow Acoustic Monitoring)

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			Comparator			*P* value
Prospective cohort study (adult patients)												
			Capnography data			**Rainbow acoustic monitoring data**			**Clinician observation data**			
			All patients received standard monitoring + capnography + rainbow acoustic monitoring									
			n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	
Tanaka 2014[56]	Respiratory pause (defined as a cessation of breathing for ≥ 20 seconds)	Not stated	45	51	88	18	51	55	8	51	16	NR

NR = not reported.
[a] Outcome based on study-reported terminology and definition.

Table 59: All Respiratory Events Detected for Each Included Study (Capnography Versus Transcutaneous Monitoring)

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
Prospective cohort studies (adult patients)									
			$ETCO_2$ capnography data			**Transcutaneous capnography data**			
			All patients received $ETCO_2$ capnography and transcutaneous capnography						
			n	**N**	**%**	**n**	**N**	**%**	
De Oliveira 2010[53]	Hypoventilation (PCO_2> 6.65 kPa; P_ECO_2 > 6.0 kPa)	Secondary	1	12	8.3	12	12	100	0.09
Kusunoki 2012[60]	Decrease in respiratory rate preceded the hypoxic event (SpO_2 < 90%)	Not stated	10	12[b]	83.3	0	12[b]	0	NR

$ETCO_2$ = end-tidal carbon dioxide; NR = not reported; PCO_2 = partial pressure of carbon dioxide; P_ECO_2 = nasal end-tidal carbon dioxide; SpO2 = arterial oxygen saturation measured by pulse oximetry.
[a] Outcome based on study-reported terminology and definition.
[b] Represents the number of hypoxic events (SpO_2 < 90% detected).

Table 60: Detailed Outcome Data for the Pooled Analysis for Other Effectiveness Outcomes: Change in Clinical Management (Including Use of Supplemental Oxygen and Ventilation Support)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Van Loon 2014[61]	Supplemental oxygen[a]	Secondary	26	206	12.6	17	209	8.1	0.134
Friederich-Rust 2014[20]	Supplemental oxygen[a]	Secondary	87	267	33	79	266	30	0.51
	Assisted ventilation[b]	Secondary	7	267	3	12	266	5	0.35
Slagelse 2013[48]	Supplemental oxygen[a]	Secondary	12	263	4.6	14	277	5.1	0.79
	Bag-mask ventilation[b]	Secondary	2	263	0.76	3	277	1.1	NR
			Standard monitoring + capnography visible			**Standard monitoring + capnography not visible**			
			n	**N**	**%**	**n**	**N**	**%**	
Beitz 2012[38]	Supplemental oxygen[a]	Secondary	32	383	8.4	45	374	12	0.118
	Assisted ventilation[b]	Secondary	0	383	0	1	374	0.3	0.494
Klare 2016[51]	Supplemental oxygen[a]	Secondary	38	121	31.4	42	117	35.9	0.463
Klare 2016[51]	Assisted ventilation[b]	Secondary	1	121	0.8	1	117	0.9	0.981
			Standard monitoring + capnography signal[c]			**Standard monitoring + delayed capnography signal[c]**			
			n	**N**	**%**	**n**	**N**	**%**	
Qadeer 2009[54]	Supplemental oxygen[a]	Secondary	65	124	52.4	82	123	66.7	0.02

NR = not reported.
[a] Included in the pooled analysis for supplemental oxygen.
[b] Included in the pooled analysis for assisted ventilation.
[c] The treatment team in the intervention group was signalled by an independent observer of abnormalities within 5 to 10 seconds of appearance on the capnography monitor (included a flat waveform for > 5 seconds, > 75% reduction in waveform amplitude compared with baseline, or respiratory rate of < 8 breaths/minute). The treatment team of the control group was signalled for prolonged apnea (> 30 seconds).[54]

Figure 7: Random Effects Meta-Analysis for Use of Supplemental Oxygen, Adults Undergoing Procedural Sedation With Capnography and Standard Monitoring Versus Standard Monitoring Alone

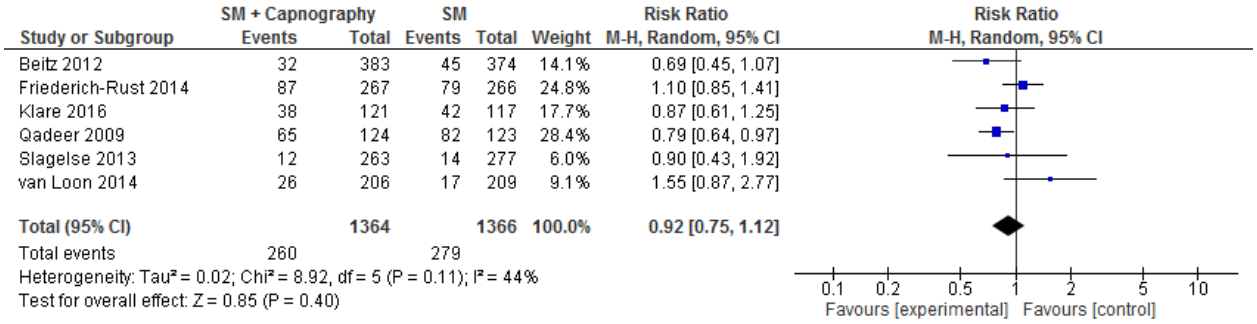
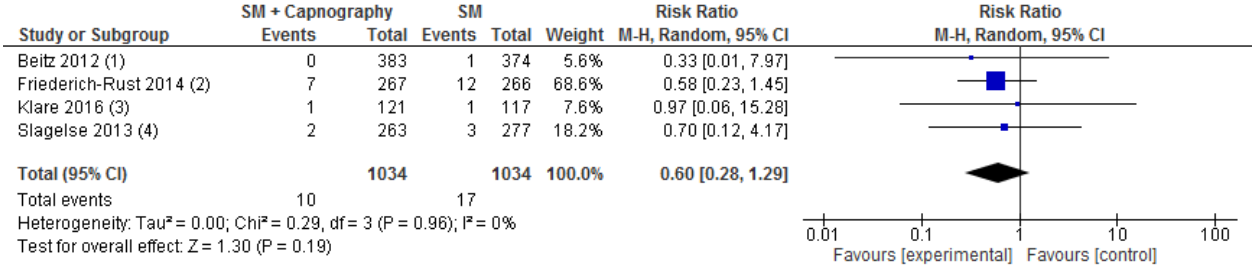


Figure 8: Random Effects Meta-Analysis for Ventilation Support, Adults Undergoing Procedural Sedation With Capnography and Standard Monitoring Versus Standard Monitoring Alone



Footnotes
(1) Assisted ventilation
(2) Assisted ventilation
(3) Assisted ventilation
(4) Bag mask ventilation

Table 61: All Other Change in Clinical Management Outcomes Reported for the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition[a]	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized studies (adult patients)									
			Standard monitoring + capnography visible			Standard monitoring			
			n	N	%	n	N	%	
van Loon 2014[61]	Chin lift or jaw thrust	Secondary	102	206	49.5	67	209	32.1	< 0.001
	Sedation prematurely terminated	Secondary	3	206	1.5	0	209	0	NR[b]
Slagelse 2013[48]	Suction	Secondary	21	263	8	23	277	8.3	0.89

Study	Definition[a]	Primary or Secondary outcome	Intervention			Comparator			*P* value
	Tongue holder or nasal airway	Secondary	12	263	5.1	9	277	3.2	0.43
	Discontinuation of procedure	Secondary	0	263	0	0	277	0	NR
			Standard monitoring + capnography visible			**Standard monitoring + capnography not visible**			
			n	**N**	**%**	**n**	**N**	**%**	
Deitch 2010[19]	Physician intervention[c]	Not stated	24	68	35.3	14	64	21.2	NR[d]
			Standard monitoring + capnography signal[e]			**Standard monitoring + delayed capnography signal[e]**			
			n	**N**	**%**	**n**	**N**	**%**	
Qadeer 2009[54]	Use of reversal drugs[f]	Other	0	124	0	0	123	0	NR
Non-randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Barnett 2016[52]	Procedure interruption (due to hemodynamic or respiratory instability)	Not stated	NR	501	1.2	NR	465	0.4	NR
			Capnography data			**Standard monitoring data**			
			All patients received standard monitoring + capnography not visible						
			n	**N[g]**	**%**	**n**	**N[h]**	**%**	
Cacho 2010[62]	Aggressive maneuvers	Not stated	0	29	0	0	11	0	NR
	Discontinuation of procedure	Not stated	0	29	0	0	11	0	NR
Deitch 2007[57]	Ventilation	Not stated	0	35	0	0	8	0	NR
	Intubation	Not stated	0	35	0	0	8	0	NR
Burton 2006[58]	Patient repositioning	Not stated	9	17	52.9	9	20	45	NR
	Physical or verbal stimulation	Not stated	17	17	100	20	20	100	NR

Study	Definition[a]	Primary or Secondary outcome	Intervention			Comparator			*P* value
	Supplemental oxygen	Not stated	13	17	76.5	14	20	70	NR
	Bag valve–mask ventilation	Not stated	4	17	23.5	4	20	20	NR

CI = confidence interval; NR = not reported.
[a] Outcome based on study-reported terminology and definition.
[b] Absolute difference and 95% CI: 1.5% −0.6% to 4.2%.
[c] Physician intervention included verbal and physical stimulation, airway realignment, supplemental oxygen, use of airway adjuncts, assisted ventilation, or intubation.
[d] Study reported a difference of13% (95% CI, –2% to 27%).
[e] The treatment team in the intervention group was signalled by an independent observer of abnormalities within 5 to 10 seconds of appearance on the capnography monitor (included a flat waveform for > 5 seconds, > 75% reduction in waveform amplitude compared with baseline, or respiratory rate of < 8 breaths/minute). The treatment team of the control group was signalled for prolonged apnea (> 30 seconds).[54]
[f] Defined in the study as a serious adverse event.
[g] Number of patients experiencing an acute respiratory event or respiratory depression detected by capnography.
[h] Number of patients experiencing an acute respiratory event or respiratory depression detected by standard monitoring.

Table 62: Study-Reported Outcomes for Survival, Neurological Functioning, and Organ Damage

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
Randomized studies (adult patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Friederich-Rust 2014[20]	Serious adverse events (for example, permanent disability or death)	Other	0	267	0	0	266	0	NR
			Standard monitoring + capnography visible			**Standard monitoring + capnography not visible**			
			n	**N**	**%**	**n**	**N**	**%**	
Beitz 2012[38]	Serious adverse events (for example, permanent disability or death)	Other	0	383	0	0	374	0	NR
Klare 2016[51]	Serious adverse events (definition NR)	Other	0	121	0	1	117	0.9	0.981
			Standard monitoring + capnography signal[b]			**Standard monitoring + delayed capnography signal[b]**			
			n	**N**	**%**	**n**	**N**	**%**	
Qadeer 2009[54]	Serious adverse events (for example, death and respiratory failure[c])	Other	0	124	0	0	123	0	NR

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
Prospective observational study (adult patients)									
			Capnography data			**Standard monitoring data**			
			All patients received standard monitoring + capnography						
			n	N	%	n	N	%	
Schlag 2013[59]	Serious adverse events (for example, permanent disability or death) due to sedation	Other	0	20	0	NA	NA	NA	NA

NA = not applicable; NR = not reported.
[a] Outcome based on study-reported terminology and definition.
[b] The treatment team in the intervention group was signalled by an independent observer of abnormalities within 5 to 10 seconds of appearance on the capnography monitor (included a flat waveform for > 5 seconds, > 75% reduction in waveform amplitude compared with baseline, or respiratory rate of < 8 breaths/minute). The treatment team of the control group was signalled for prolonged apnea (> 30 seconds).[54]
[c] Definition of respiratory failure was not provided.[54]

Research Question 2: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Procedural Sedation

Table 63: All SpO_2 Outcomes Reported for Each Included Study

Study	Definition[a]	Primary or Secondary outcome[a]	Intervention			Comparator			*P* value
Randomized studies (pediatric patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Langhan 2015[68]	SpO_2 < 95% (oxygen desaturation)	Primary	23	77	29.9	23	77	29.9	1
			Standard monitoring + capnography signal[b]			Standard monitoring + delayed capnography signal[b]			
			n	N	%	n	N	%	
Lightdale 2006[65]	SpO_2 < 95% for > 5 seconds (oxygen desaturation)	Primary	9	83	10.8	20	80	25	0.024

$ETCO_2$ = end-tidal carbon dioxide; SpO_2 = arterial oxygen saturation measured by pulse oximetry.
[a] Outcome based on study-reported terminology and definition.
[b] The treatment team in the intervention group was signalled by an independent observer after 15 seconds of alveolar hypoventilation (absence of $ETCO_2$ waveform); the treatment in the control group was signalled by an independent observer after 60 seconds of alveolar hypoventilation.

Table 64: All Respiratory Events Detected for Each Included Study (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized studies (pediatric patients)									
			Standard monitoring + capnography visible			**Standard monitoring**			
			n	**N**	**%**	**n**	**N**	**%**	
Langhan 2015[68]	Hypoventilation ($ETCO_2$ < 30 mm Hg without > 50 mm Hg)	Primary	34	77	44.2	36	77	46.8	0.87
Non-randomized studies (pediatric patients)									
			Capnography data			Standard monitoring data			
			All patients received standard monitoring + capnography not visible						
			n	N	%	n	N	%	
Kannikeswaran 2011[67]	$ETCO_2$ abnormalities ($ETCO_2$ change from baseline ≥ 10 mm Hg)	Not Stated	64[a]	150	42.7	NA[a]	NA	NA	NA
Anderson 2007[66]	Adverse airway and respiratory events (based on 14 events detected from 31 patients)[b]	Not stated	11[c]	14	79	14[c]	14	100	NR

$ETCO_2$ = end-tidal carbon dioxide; mm Hg = millimetres of mercury.
[a] Hypoxia occurred in 27 of the 150 patients; for 19 of the 27 episodes (70.4%), $ETCO_2$ abnormalities were documented prior to pulse oximetry and respiratory rate.[67]
[b] Adverse airway and respiratory events defined as apnea (cessation of breathing for 30 seconds or no CO_2 waveform), hypoxemia, hypercarbia, or airway obstruction with or without oxygen desaturation.
[c] In 11 of the 14 patients with acute respiratory events, $ETCO_2$ abnormalities were detected before changes in pulse oximetry and clinical observation.[58]

Table 65: Change in Clinical Management Outcomes Reported for the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			P value
Randomized studies (pediatric patients)									
			Standard monitoring + capnography visible			Standard monitoring			
			n	N	%	n	N	%	
Langhan 2015[68]	Any intervention	Primary	38	77	49.4	39	77	50.7	0.87[a]
	Supplemental oxygen		4	77	5.22	2	77	2.6	0.68
	Shoulder roll		13	77	16.9	11	77	14.3	0.68
	Head tilt or jaw thrust		3	77	3.9	11	77	14.3	0.02
	Verbal or physical stimulation		28	77	36.4	33	77	42.9	0.41[b]
	Bag-valve mask ventilation		0	77	0	0	77	0	NR
	Use of reversal drugs		0	77	0	0	77	0	NR
	Intubation		0	77	0	0	77	0	NR

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			P value
			Standard monitoring + capnography[c]			Standard monitoring + delayed capnography[c]			
			n	N	%	n	N	%	
Lightdale 2006[65]	Procedures terminated due to safety concerns	Secondary	0	83	0	0	80	0	NR
	Bag-mask ventilation		0	83	0	0	80	0	NR
	Sedation reversal		0	83	0	0	80	0	NR
Non-randomized studies (pediatric patients)									
			Capnography data			Standard monitoring data			
			All patients received standard monitoring + capnography not visible						
			n	N[d]	%[e]	n	N[f]	%[e]	
Anderson 2007[66]	Intubation[g]	Not stated	0	11	0	0	14	0	NR
	Jaw thrust		2	11	18.2	4	14	28.6	NR
	Jaw thrust with supplemental oxygen		5	11	45.5	6	14	42.8	NR
	Bag valve–mask ventilation		4	11	36.4	4	14	28.6	NR

CI = confidence interval; $ETCO_2$ = end-tidal carbon dioxide; NR = not reported; OR = odds ratio.
[a] Adjusted analysis: controlling for patient age and length of sedation, the odds of a patient receiving any intervention was statistically significantly lower in the capnography group versus the comparator group (OR 0.25; 95% CI, 0.13 to 0.50). The odds of receiving a timely intervention were higher in the capnography group versus the comparator group (OR 2.26; 95% CI, 1.34 to 3.81).
[b] Adjusted analysis: controlling for patient age and length of sedation, the odds of verbal or physical stimulation was statistically significantly lower in the capnography group versus the comparator group (OR 0.31; 95% CI, 0.17 to 0.57).
[c] The treatment team in the intervention group was signalled by an independent observer after 15 seconds of alveolar hypoventilation (absence of $ETCO_2$ waveform); the treatment in the control group was signalled by an independent observer after 60 seconds of alveolar hypoventilation.
[d] Number of patients experiencing an adverse airway and respiratory event detected by capnography.
[e] Percentages calculated by CADTH.
[f] Number of patients experiencing an adverse airway and respiratory event detected clinically.
[g] Defined in the study as a serious adverse event.

Table 66: Adverse Events Related to the Capnography Device Reported In The Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized studies (pediatric patients)									
			Standard monitoring + Capnography[b]			**Standard monitoring + Delayed Capnography[b]**			
			n	**N**	**%**	**n**	**N**	**%**	
Lightdale 2006[65]	Adverse events	Secondary	0[a]	83	0	0	80	0	NR
Non-randomized studies (pediatric patients)									
			Capnography data			Standard monitoring data			
			All patients received standard monitoring + capnography not visible						
			n	N	%	n	N	%	
Anderson 2007[66]	Serious adverse events (aspiration, laryngospasm, anaphylaxis, or death)	Not stated	0	125	0	0	125	0	NR

$ETCO_2$ = end-tidal carbon dioxide; NR = not reported.
[a] Two patients had adverse events, neither related to capnography or study participation.
[b] The treatment team in the intervention group was signalled by an independent observer after 15 seconds of alveolar hypoventilation (absence of $ETCO_2$ waveform); the treatment in the control group was signalled by an independent observer after 60 seconds of alveolar hypoventilation.

Research Question 3: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients Undergoing Cardiopulmonary Resuscitation

Table 67: Survival of a CPR Event (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Retrospective cohort study (adult patients)									
			Documented use of $ETCO_2$			**No documented use of $ETCO_2$**			
			n	**N**	**%**	**n**	**N**	**%**	
Chen 2015[1]	Survival of the acute event	Not stated	15	53	28.3	150	1,060	14.2	NR

CPR = cardiopulmonary resuscitation; $ETCO_2$ = end-tidal carbon dioxide; NR = not reported.

Table 68: Return of Spontaneous Circulation (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Retrospective cohort study (adult patients)									
			Documented use of $ETCO_2$			**No documented use of $ETCO_2$**			
			n	**N**	**%**	**n**	**N**	**%**	
Chen 2015[1]	Return of spontaneous circulation[a]	Not stated	15	53	28.3	150	1,060	14.2	NR[b]

$ETCO_2$ = end-tidal carbon dioxide; NR = not reported; OR = odds ratio; RD = risk difference.
[a] Sustained return of spontaneous circulation.
[b] OR 2.39 (1.29 to 4.46); RD 0.14 (0.02 to 0.26).

Table 69: Survival to Hospital Discharge (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Retrospective cohort study (adult patients)									
			Documented use of $ETCO_2$			**No documented use of $ETCO_2$**			
			n	**N**	**%**	**n**	**N**	**%**	
Chen 2015[1]	Survival to hospital discharge[a]	Not stated	1	53	1.9	22	1060	2.1	0.924[b]

$ETCO_2$ = end-tidal carbon dioxide.
[a] Survival to hospital discharge was defined as a patient having had a record of survival to discharge.
[b] Reported odds ratio was 0.91 (0.12 to 6.90).

Research Question 4: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients Undergoing Cardiopulmonary Resuscitation

No data available.

Research Question 5: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients in Serious or Critical Condition

Table 70: Survival-Related Outcomes Reported in the Included Studies (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			OR (95% CI)
Retrospective cohort study (adult patients)									
			Capnography			No capnography			
			n	N	%	n	N	%	
Bhat 2014[69]	Mortality[a]	Not stated	NR	10	NR	NR	159	NR	< 0.001 (< 0.001 to > 100)

CI = confidence interval; NR = not reported; OR = odds ratio.
[a] Time point of assessment not specified.

Table 71: ETT Placement Outcomes Reported for the Included Studies (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Prospective cohort study (adult patients)									
			Capnography			No capnography			
			n	N	%	n	N	%	
Silvestri 2005[70]	Unrecognized misplaced ETT	Primary	0	93	0	14	60	23.3	NR[a]
	Death due to unrecognized improper tube placement	Not stated	0	93	0	9	60	15	NR

CI = confidence interval; ETT = endotracheal tube; NR = not reported; OR = odds ratio.
[a] Odds of unrecognized misplaced intubation was higher in the comparator group versus the intervention group: OR 28.6 (95% CI, 4.0 to 122.0).

Research Question 6: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients in Serious or Critical Condition

Table 72: Respiratory Failure-Related Outcomes Reported in the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (pediatric patients)									
			Standard monitoring + capnography visible			Standard monitoring + capnography not visible			
			n	N	%	n	N	%	
Kong 2013[71]	PCO_2 abnormalities (PCO_2 > 60 mm Hg or < 40 mm Hg)	Primary	9	24	37.5	8	24	33.3	0.763
Prospective cohort study with historical control (pediatric patients)									
			Capnography			**No Capnography**			
			n	**N**	**%**	**n**	**N**	**%**	
Hawkes 2015[73]	Normocapnia[a]	Not stated	25	44	56.8	23	48	47.9	0.396

mm Hg = millimetres of mercury; PCO_2 = partial pressure of carbon dioxide.
[a] PCO_2 within target range (5 and 8 kPa) within the first 10 minutes of life.

Table 73: Respiratory Events Detected for the Included Study (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (pediatric patients)									
			Standard monitoring + capnography visible			Standard monitoring + capnography not visible			
			n	N	%	n	N	%	
Kong 2013[71]	$ETCO_2$ abnormalities ($ETCO_2$ > 60 mm Hg or < 40 mm Hg)	Primary	8	24	33.3	12	24	52.6	0.236
Kugelman 2015[72]	Hypercarbia; hypocarbia[a]	Primary	NR	NR	3.8%; 3.8%	NR	NR	8.8%; 8.9%	0.03

$ETCO_2$ = end-tidal carbon dioxide; NR = not reported.
[a] Percentage of time in unsafe $ETCO_2$ high range; and percentage of time in unsafe $ETCO_2$ low range.

Table 74: Change in Clinical Management Outcomes Reported for the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention		Comparator		*P* value
Randomized study (pediatric patients)							
			Standard monitoring + capnography visible		Standard monitoring + capnography not visible		
			Mean or Median	Range or SD	Mean or Median	Range or SD	
Kong 2013[71]	Ventilator days	Secondary	1	0 to 30	1.5	0 to 38	0.562
	Duration of CPAP (minutes)	Secondary	5.2	4.1	6	3.7	NR[a]
	Duration of PPV (minutes)	Secondary	6.4	9	5.9	9	NR[a]
Kugelman 2015[72]	Number of days of ventilation	Secondary	5	0.25 to 52	6	0.8 to 107	0.62
	Number of ABG samples taken per hour of recording	Secondary	0.22	0.09 to 0.72	0.23	0.13 to 0.39	0.43
	Number of ventilator setting changes per hour of recording	Secondary	0.05	0.0 to 0.24	0.04	0.0 to 0.18	0.94

ABG = arterial blood–gas analysis; CPAP = continuous positive airway pressure; NR = not reported; PPV = positive pressure ventilation; RCT = randomized controlled trial; SD = standard deviation.
[a] Statistical testing was not performed.

Table 75: Survival-Related Outcomes Reported in the Included Studies (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (pediatric patients)									
			Standard monitoring + capnography visible			Standard monitoring + capnography not visible			
			n	N	%	n	N	%	
Kong 2013[71]	Survival to hospital discharge	Secondary	21	24	87.5	23	24	95.8	0.609

Table 76: Length of Stay in Hospital Reported in the Included Studies (Capnography Versus No Capnography)

Study	Definition	Primary or Secondary outcome	Intervention		Comparator		*P* value
Randomized study (pediatric patients)							
			Standard monitoring + capnography visible		Standard monitoring + capnography not visible		
			Median	Range	Median	Range	
Kugelman 2015[72]	Length of stay in hospital (days)	Secondary	51	8 to 166	58	5 to 213	0.87

Research Question 7: Clinical Effectiveness of $ETCO_2$ Monitoring for Adult Patients With Known Obstructive Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

Table 77: All Respiratory Events Detected for Each Included Study (Capnography Versus Pulse Oximetry and Respiratory Rate)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (adult patients)									
			Continuous capnography			Pulse oximetry and respiratory rate every 4 hours			
			n	N	%	n	N	%	
Hutchison 2008[32]	Respiratory depression[a]	Primary	15	29	52	2	25	8	NR
	Pauses in breathing while sleeping	Secondary	7	29	24	12	25	48	NR

$ETCO_2$ = end-tidal carbon dioxide; mm Hg = millimetres of mercury; NR = not reported; RR = respiratory rate; SpO_2 = arterial oxygen saturation measured by pulse oximetry.
[a] Respiratory depression was defined as RR < 6 breaths/minute, apnea > 20 seconds, $ETCO_2$ > 60 mm Hg, SpO_2 < 88%. All episodes reported were detected by the first 2 measures.

Table 78: All Respiratory Events Detected for Each Included Study (Capnography Versus Rainbow Acoustic Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Prospective cohort study (adult patients)									
			Capnography			Rainbow acoustic monitoring			
			All patients were monitored with standard monitoring + capnography + rainbow acoustic monitoring						
			n	N	%	n	N	%	
Ramsay 2013[74]	Respiratory pause[b]	Not stated	13	21	62	17	21	81	0.0461

[b] Respiratory pause was defined as no inspiration or expiration for ≥ 30 seconds (as measured by the manual annotation of acoustic and capnography data and breathing sounds).

Table 79: Change in Clinical Management Outcomes Reported for the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (adult patients)									
			Continuous capnography			Pulse oximetry and respiratory rate every 4 hours			
			n	N	%	n	N	%	
Hutchison 2008[32]	Use of reversal drug[a]	Not stated	0	29	0	0	25	0	NR

NR = not reported.
[a] Study defined as the need of naloxone (Narcan) for the reversal of opioid-induced respiratory depression.

Table 80: Survival-Related Outcomes Reported in the Included Study (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Randomized study (adult patients)									
			Capnography only			Pulse oximetry and respiratory rate			
			n	N	%	n	N	%	
Hutchison 2008[32]	Survival to hospital discharge	Secondary	29	29	100	25	25	100	NR

NR = not reported.

Table 81: Reported Outcomes Related to the Length of Stay in Hospital Reported by the Included Studies (Capnography Versus Standard Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention		Comparator		*P* value
Randomized study (adult patients)							
			Capnography only		**Pulse oximetry and respiratory rate**		
			Mean	**SD**	**Mean**	**SD**	
Hutchison 2008[32]	Length of stay in hospital (days)	Secondary	3.9	1.5	3.8	1.4	0.03
	Total time in the post-anesthesia care unit (hours)	Secondary	2.9	NR	2.1	NR	0.03

NR = not reported; SD = standard deviation.

Table 82: Adverse Events Related to the Capnography Device Reported in the Included Studies (Capnography Versus Rainbow Acoustic Monitoring)

Study	Definition	Primary or Secondary outcome	Intervention			Comparator			*P* value
Prospective cohort study (adult patients)									
			Capnography			**Rainbow acoustic monitoring**			
			All patients were monitored with standard monitoring + capnography + rainbow acoustic monitoring						
			n	**N**	**%**	**n**	**N**	**%**	
Ramsay 2013[74]	Capnography not reliably functioning	Not stated	2	33	6.1	NA	NA	NA	NA
	% of time that the device did not provide data	Not stated	NR	NR	< 2	NR	NR	< 2	NR

NA = not available; NR = not reported.

Research Question 8: Clinical Effectiveness of $ETCO_2$ Monitoring for Pediatric Patients With Known Sleep Apnea or Receiving High Doses of Opioids in Post-Operative Care

No data available.

APPENDIX 12: Clinical and Cost Inputs for the Economic Model

Table 83: Clinical Inputs for Each Clinical Condition in the Adult Population (Primary Analysis)

Variable	Input	Range		Distribution	Source
		Low limit	High limit		
Sedation — adults					
Proportion of patients who experience respiratory event(s)	58.27%	46.61%	69.92%	Beta (α = 451; β = 323)	Clinical review
Respiratory failure (progressing due to respiratory event): mainly hypoxemia (PaO_2< 8.0 kPa or < 60 mm Hg) but also hypercapnia					
SM	28.25%	22.6%	33.9%	Beta (α = 404; β = 1026)	Clinical review
Capnography (RR compared with SM)	0.70	95% CI, 0.59 to 0.83		Lognormal	Clinical review
Survival to hospital discharge	100.00%			None	Clinical review
Discharge w/ organ damage	0.00%			None	Clinical review
Rate of ventilation assistance					
SM	7.08%	5.66%	8.50%	Beta (α = 17; β = 223)	Clinical review
Capnography (RR compared with SM)	0.60	95% CI, 0.28 to 1.29		Lognormal	Clinical review
Supplemental oxygen					
SM	74.01%	59.21%	88.81%	Beta (α = 279; β = 98)	Clinical review
Capnography (RR compared with SM)	0.92	95% CI, 0.75 to 1.12		Lognormal	Clinical review
CPR — adults					
Probability of correct ETT placement[a]	93.00%	89%	97%	Beta	Takeda 2003,[147] Grmec 2002[148]
Undetected ETT misplacements (i.e., false negatives)					
Capnography	0.00%			None	Grmec 2002[148]

Variable	Input	Range		Distribution	Source
		Low limit	High limit		
SM	0.00%	0	0.2[a]	None	Grmec 2002[148]
Survival given undetected ETT misplacement	0.00%				Assumption
Probability of survival of acute event (i.e., return to spontaneous circulation)					
Capnography	28.3%	22.6%	34.0%	Beta (α = 15; β = 38)	Chen, 2015;[1] Phelan 2013[83]
SM	14.2%	11.4%	17.0%	Beta (α = 150; β = 910)	Chen, 2015;[1] Phelan 2013[83]
Probability of survival to hospital discharge					
Capnography	1.9%	1.5%	2.3%	Beta (α = 1; β = 52)	Chen, 2015;[1] Phelan 2013[83]
SM	2.1%	1.7%	2.5%	Beta (α = 22; β = 1028)	Chen, 2015;[1] Phelan 2013[83]
Probability of discharge w/ organ damage[a]	10.70%	8.56%	12.84%	Beta	Girotra 2012[149]

CI = confidence interval; CPR = cardiopulmonary resuscitation; ETT = endotracheal tube; mm Hg = millimetres of mercury; PaO_2 = partial pressure of oxygen; RR = relative risk; SM = standard monitoring.
[a] The high and low ranges for this parameter were based on ± 20% of the mean.

Table 84: Clinical Inputs for Each Clinical Condition in the Adult Population (Exploratory Analysis)

Variable	Input	Range		Distribution	Source
Serious and critical condition — adults					
Probability of correct ETT placement[a]	92.00%	73.60%	100.00%	Beta (α = 274; β = 23)	Schwartz 1995[150]
Undetected ETT misplacements (i.e., false negatives)					
SM	23.00%	13.40%	36.00%	Beta (α = 14; β = 46)	Silvestri, 2005[70]
Capnography	0.00%				Silvestri, 2005[70]
Survival given undetected ETT misplacement	35.71%	28.57%	42.86%	Beta (α = 5; β = 9)	Silvestri 2005[70]
Organ damage in those alive with ETT misplacement	40.00%	32.00%	48.00%	Beta (α = 2; β = 3)	Silvestri 2005[70]
Proportion of patients who experience respiratory event(s)[b]	58.27%	30.00%	90.00%	Beta (α = 451; β = 323)	GS
Respiratory failure (progressing due to respiratory event): mainly hypoxemia (PaO_2< 8.0 kPa or < 60 mm Hg) but also hypercapnia					
SM	20.85%	16.68%	25.02%	Beta (α = 741; β = 2813)	Thomas 2014[151]

Variable	Input	Range		Distribution	Source
Capnography (RR compared with SM)[c]	0.70	0.1	0.9	Lognormal	GS
Survival to hospital discharge[d,e] (assumed no difference between monitoring modalities, as per clinical review)	41.00%	32.80%	49.20%	Beta	Luhr 1999[152]
Discharge w/ organ damage	0.00%			None	Silvestri 2005[70]
Rate of ventilation assistance					
SM	7.08%	5.66%	8.50%	Beta (α = 17; β = 223)	GS
Capnography (RR compared with SM)	0.60	95% CI, 0.28 to 1.29		Lognormal	GS
Supplemental oxygen					
SM	74.01%	59.21%	88.81%	Beta (α = 279; β = 98)	GS
Capnography (RR compared with SM)	0.92	95% CI, 0.75 to 1.12		Lognormal	GS
Post-operative care — adults					
Proportion of patients who experience respiratory event(s)	51.70%	41.36%	62.04%	Beta (α = 15; β = 14)	Hutchison 2008[32]
Critical respiratory event (defined as Hb oxygen saturation < 90%, respiratory rate < 8 breaths, upper airway obstruction)					
SM[e]	3.85%	0.80%	6.90%	Beta	Karcz 2013[153]
Capnography (RR compared with SM)[c]	0.70	0.1	0.9	Lognormal	GS
Survival to hospital discharge	99.10%	79.28%	100%	Beta (322, 3)	Rose 1994[154]
Discharge w/ organ damage	0.00%			None	GS
Rate of ventilation assistance					
SM	24.60%	19.68%	29.52%	Beta (80, 245)	Rose 1994[154]
Capnography (RR compared with SM)	0.60	95% CI: 0.28 to 1.29		Lognormal	GS
Supplemental oxygen					
SM	59.70%	47.76%	71.64%	Beta (194, 131)	Rose 1994[154]
Capnography (RR compared with SM)	0.92	95% CI: 0.75 to 1.12		Lognormal	GS

CI = confidence interval; ETT = endotracheal tube; GS = data generalized from adult patients receiving procedural sedation; Hb = hemoglobin; mm Hg = millimetres of mercury; PaO_2 = partial pressure of oxygen; RR = relative risk; SM = standard monitoring.

[a] Range assumed to test capnography benefit in detecting ETT misplacement

[b] Assume wider range from 46.61 to 69.92%, to, 30 to 90% to test impact in sensitivity analysis.

[c] Assume wider range from (95% CI, 0.59 to 0.83) to (0.1 to 0.9) to test impact in sensitivity analysis.

[d] 90-day mortality converted to 30-day mortality.

[e] The high and low ranges for this parameter were based on ± 20% of the mean.

Table 85: Clinical Inputs For Each Clinical Condition In The Pediatric Population

Variable	Input	Range		Distribution	Source
Sedation — pediatrics					
Proportion of patients who experience respiratory event(s)	46.75%	37.40%	56.10%	Beta (α = 36; β = 41)	Langhan 2011[77]
Respiratory failure (progressing due to respiratory event): mainly hypoxemia (PaO_2< 8.0 kPa or < 60 mm Hg) but also hypercapnia					
SM	12.07%	9.66%	14.48%	Beta (α = 7; β = 51)	Langhan 2011[77]
Capnography (RR compared with SM)	1			None	Assumption (based on clinical review)
Survival to hospital discharge	100.00%			None	Assumption
Discharge w/ organ damage	0.00%			None	Assumption
Serious and critical condition — neonates					
Probability of correct ETT placement	73.30%	58.64%	87.96%	Beta (33,12)	Aziz 1999[155]
Undetected ETT misplacements (i.e., false negatives)					
SM	8.33%	6.67%	10.00%	Beta (5,55)	Roberts1995[82]
Capnography	2.50%	2.00%	3.00%	Beta (1,39)	Roberts 1995[82]

ETT = endotracheal tube; PaO_2 = partial pressure of oxygen; RR = relative risk; SM = standard monitoring.

Table 86: Cost Inputs for Each Population (in 2015 Dollars)

Item	Cost	Low limit	High limit	SD	Distribution	Source
Capnography purchase price	5000.00	3000.00	7000.00		None	BC program[a] — 2015
Number of patients a capnography serves per month	4	4	60		None	BC program[a] — 2015
Capnography cost per patient	20.83	16.67	25.00		None	BC program[a] — 2015
Maintenance and consumable supplies per patient	27.50	20.00	40.00	5.10	Gamma	BC program[a] — 2015
Non-traumatic brain injury[b]	31312.67	25050.14	37575.21	87614.73	Lognormal	Chen 2012[84]
Intubation	158.28	126.63	189.94	31.41	Gamma	Saunders et al. 2015[85]
Supplemental O_2 (per procedure)	12.56	10.05	15.07	2.51	Gamma	Saunders et al. 2015[85]
Respiratory failure, hospital						
Sedation — adults	851.04	74.87	2053.26	607.43	Gamma	OCCI[156] - Nov 2015
SCC — adults	28493.54	504.09	461740.10	44435.54	Gamma	OCCI[156] - Nov 2015

Item	Cost	Low limit	High limit	SD	Distribution	Source
Post-operative care — adults	7962.04	333.25	62602.70	14277.88	Gamma	OCCI[156] Nov 2015
Respiratory failure, physician						
Sedation — adults	325.40				None	Fee schedule[157] Nov 2015[c]
SCC — adults	3100.90				None	Fee schedule[157] Nov 2015[c]
Post-operative care — adults	965.90				None	Fee schedule[157] Nov 2015[c]
Death in hospital (due to respiratory failure)						
CPR — adults	949.12	54.84	5834.96	1192.72	Gamma	OCCI[156] - Nov 2015
SCC — adults	53026.11	182.44	631150.09	87685.75	Gamma	OCCI[156] - Nov 2015
Post-operative care — adults	53026.11	182.44	631150.09	87685.75	Gamma	OCCI[156] - Nov 2015

BC = British Columbia; CPR = cardiopulmonary resuscitation; O_2 = oxygen; OCCI = Ontario Case Costing Initiative; SCC = serious or critical condition; SD = standard deviation.

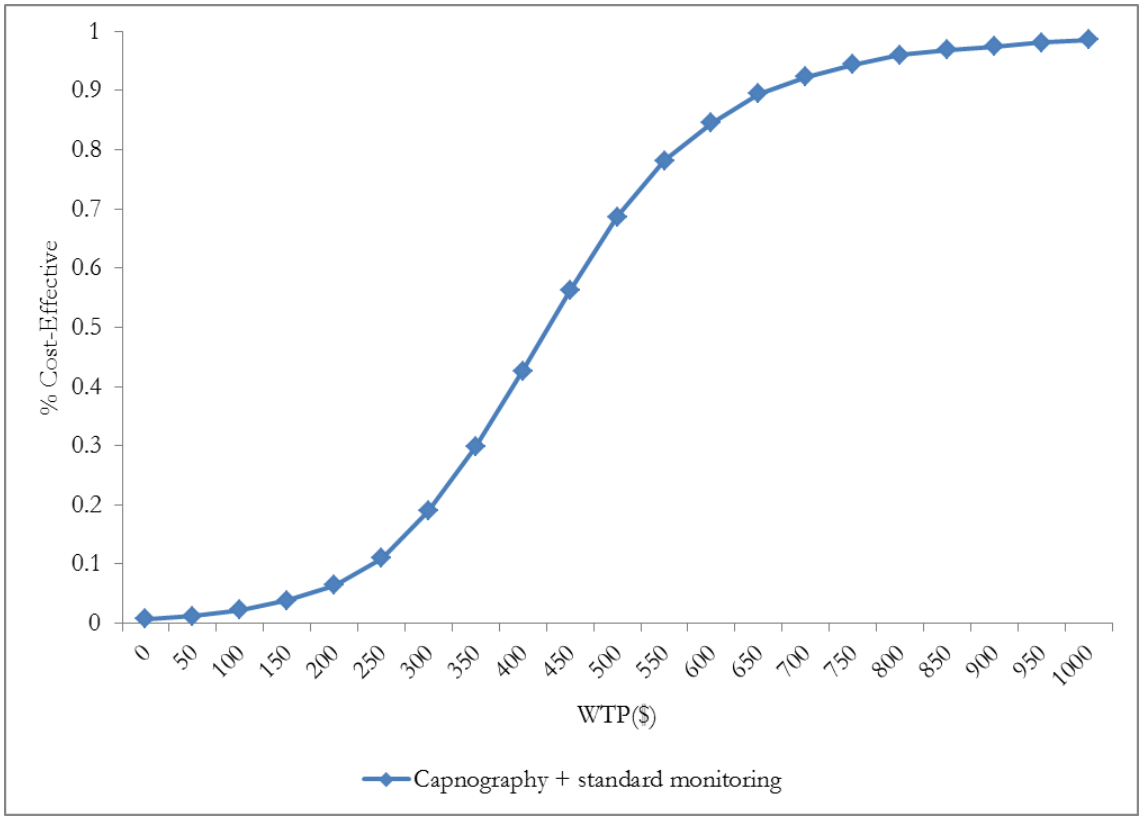
[a] Richard Milo, personal communication, November 2015.

[b] This included annual cost of hospital emergency department, acute care, and physician services for treatment of non-traumatic brain injury.

[c] Fee schedule refers to the Ontario Schedule of Benefits for Physician Services.

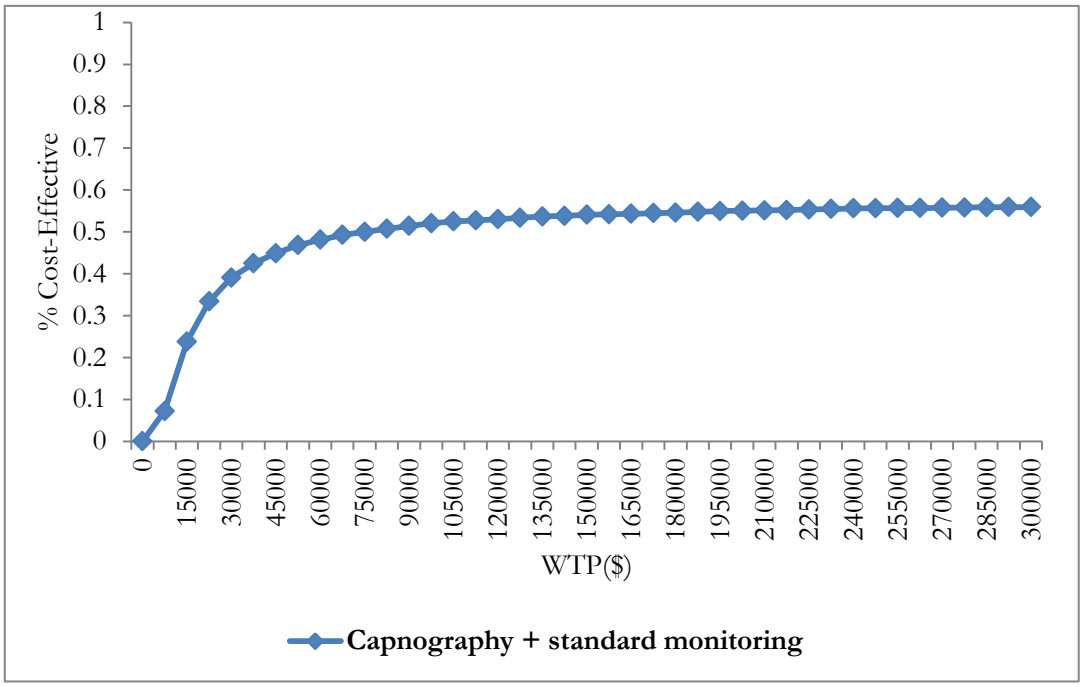
APPENDIX 13: Detailed Economic Results

Figure 9: Cost-Effectiveness Acceptability Curve of Capnography With Standard Monitoring, Adult Patients Undergoing Procedural Sedation



WTP = willingness to pay.

Figure 10: Cost-Effectiveness Acceptability Curve of Capnography With Standard Monitoring, Adult Patients Undergoing CPR (Using Data from Chen et al.[1])



CPR = cardiopulmonary resuscitation; WTP = willingness to pay.

Figure 11: Tornado Diagram, Adult Patients Undergoing Procedural Sedation

Note: See

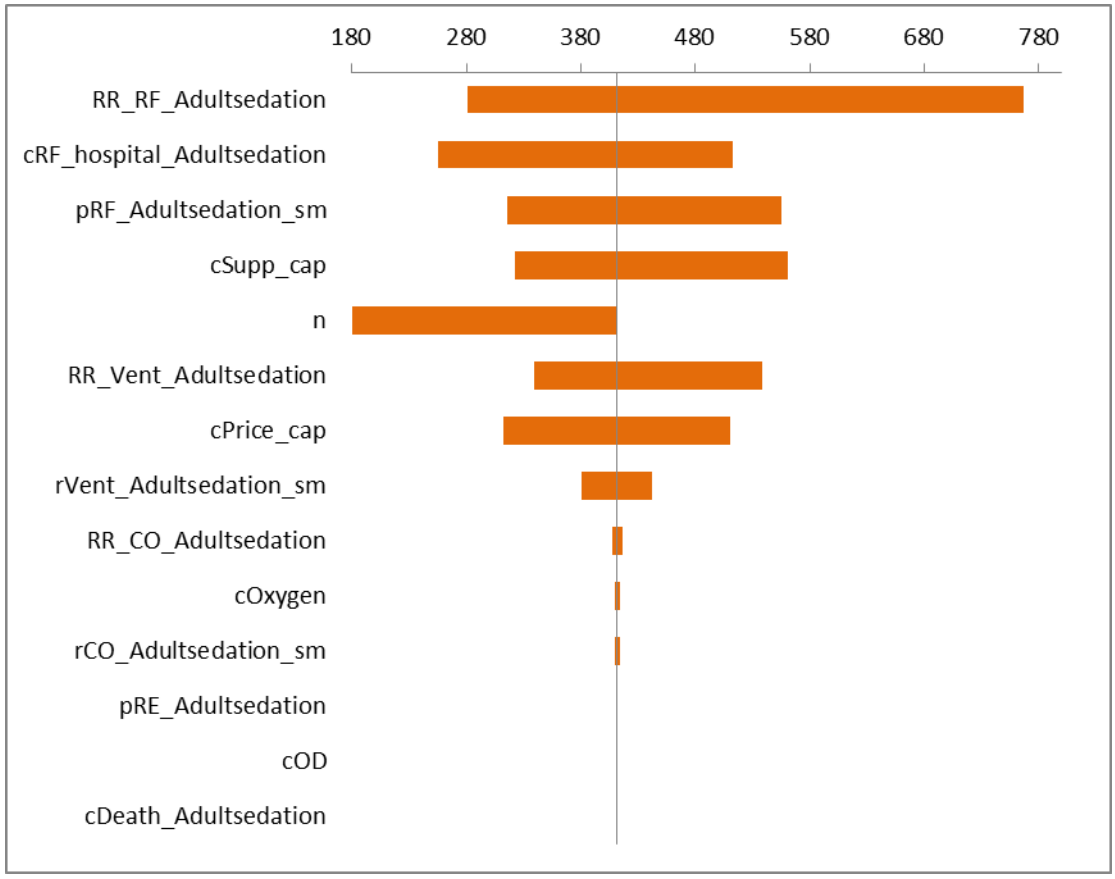


Table 87 for a description of each variable.

Figure 12: Tornado Diagram, Adult Patients Undergoing CPR. Negative ICERs Represent Situation in Which Capnography is Dominated by Standard Monitoring

Note: See

Table 87 for a description of each variable.

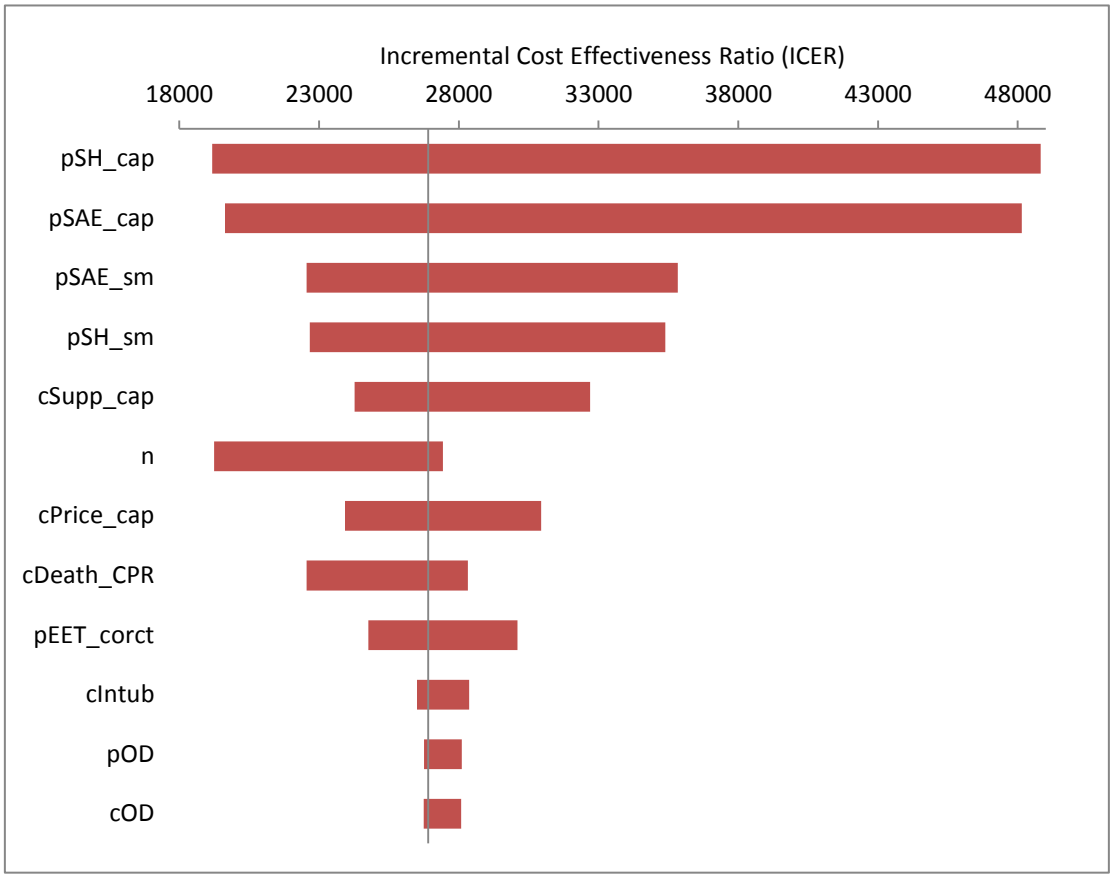


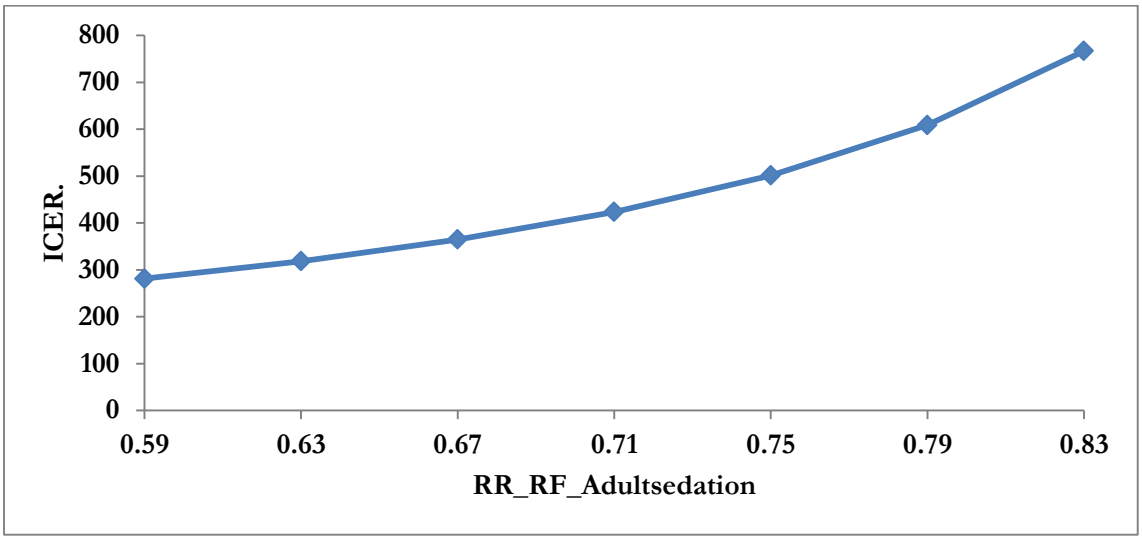
Table 87: Variable Description Used in Tornado Diagram Analysis

Variable	Description
cDeath_Adultsedation	Cost of death in hospital due to RF, adult patients undergoing procedural sedation
cDeath_CPR	Cost of death in hospital due to RF, adult patients undergoing CPR
cDeath_NanSCC	Cost of death in hospital due to RF, neonatal patients in serious or critical condition
cIntub	Cost of Intubation
cOD	Cost of treating organ damage (i.e., nTBI)
cOxygen	Cost of oxygen supplementation
cPrice_cap	Purchase price of capnography
cRF_hospital_Adultsedation	Hospital cost of respiratory failure, adult patients undergoing procedural sedation
cSupp_cap	Cost of capnography maintenance and consumables
n	Number of patients served per month per device
pEET_corct	Probability ET tube placed correctly
pEET_MisP_nonDectect_cap	ET tube misplacement (not detected; i.e., false negatives), capnography
pEET_MisP_nonDectect_sm	ET tube misplacement (not detected; i.e., false negatives), standard monitoring

Variable	Description
pOD	Probability of discharge with organ damage
pRE_Adultsedation	Proportion of patients who experience respiratory events
pRF_Adultsedation_sm	Probability of respiratory failure, adult patients undergoing procedural sedation, standard monitoring
pSAE_cap	Proability of survival of acute event, capnography
pSAE_sm	Proability of survival of acute event, standard monitoring
pSH_cap	Probability of survival to hospital discharge, capnography
pSH_sm	Probability of survival to hospital discharge, standard monitoring
rCO_Adultsedation_sm	Rate of supplemental oxygen, adult patients undergoing procedural sedation, standard monitoring
RR_CO_Adultsedation	Relative risk of supplemental oxygen, capnography vs. standard monitoring, adult patients undergoing procedural sedation
RR_RF_Adultsedation	Relative risk of respiratory failure, capnography vs. standard monitoring, adult patients undergoing procedural sedation
RR_Vent_Adultsedation	Relative risk of ventilation assistance, capnography vs. standard monitoring, adult patients undergoing procedural sedation
rVent_Adultsedation_sm	Rate of ventilation assistance, standard monitoring, adult patients undergoing procedural sedation

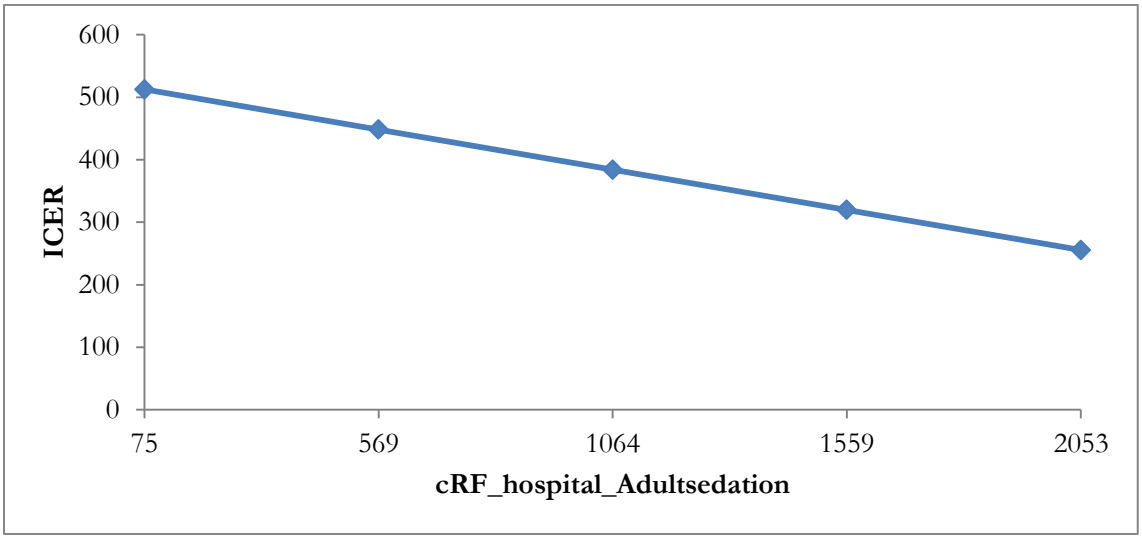
CPR = cardiopulmonary resuscitation; ET = endotracheal tube; nTBI = non-traumatic brain injury; RF = respiratory failure ; vs. = versus.

Figure 13: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Relative Risk of Respiratory Failure Using Capnography and Standard Monitoring Compared With Standard Monitoring Alone, Adult Patients Undergoing Procedural Sedation



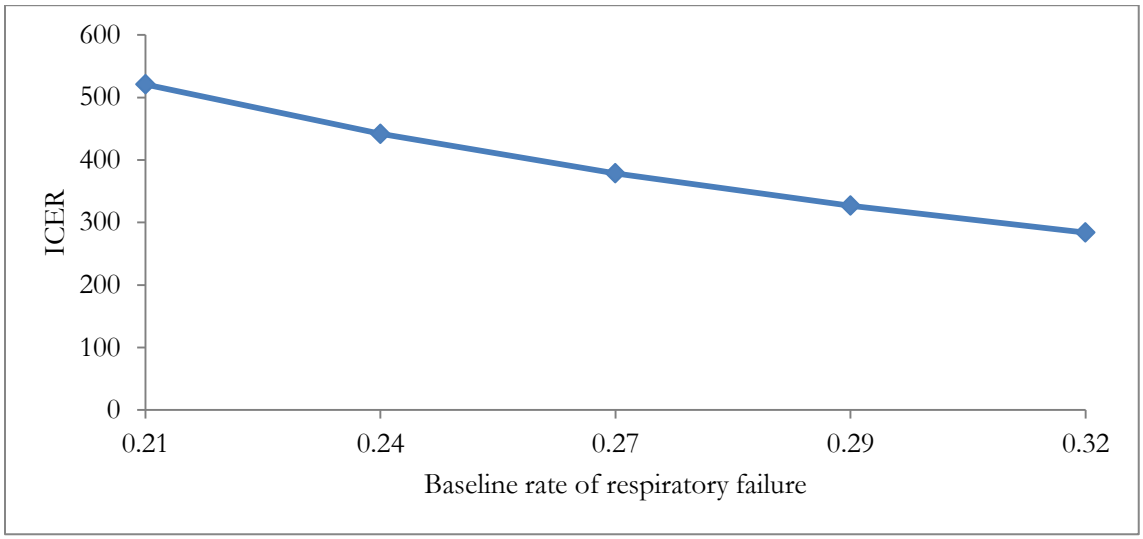
ICER = incremental cost-effectiveness ratio.

Figure 14: One-Way Sensitivity Analysis on the Impact to the ICER When Varying Hospital Cost for Respiratory Failure, Adult Patients Undergoing Procedural Sedation



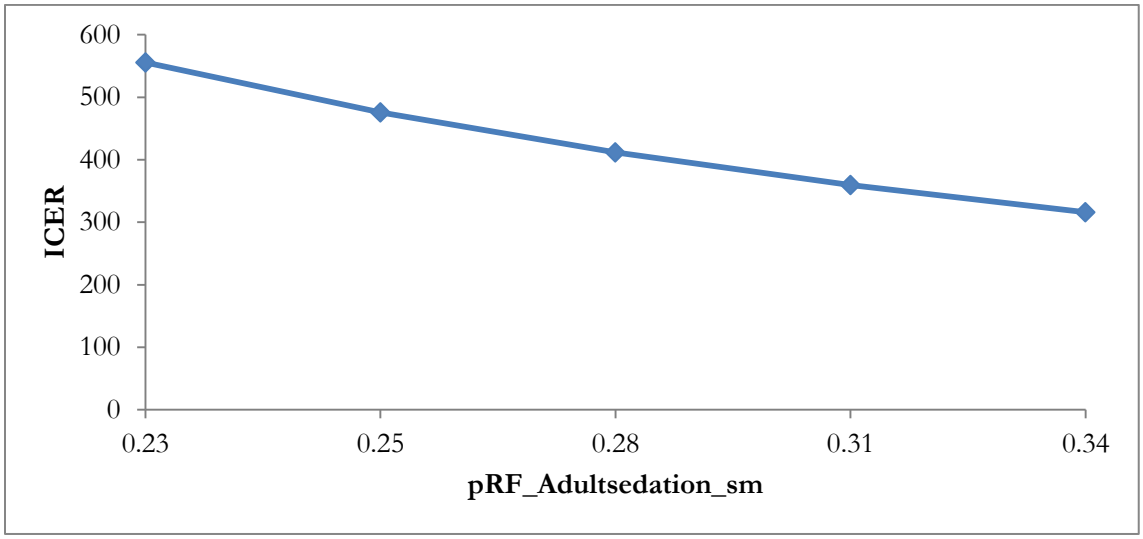
ICER = incremental cost-effectiveness ratio.

Figure 15: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Baseline Rate of Respiratory Failure, Adult Patients Undergoing Procedural Sedation



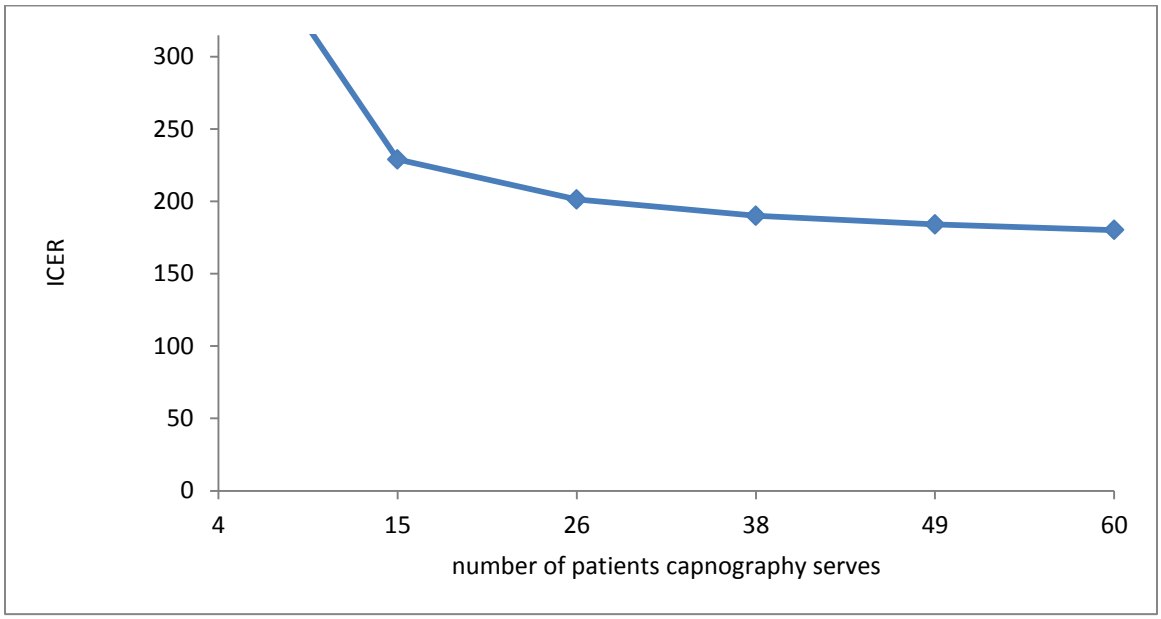
ICER = incremental cost-effectiveness ratio.

Figure 16: One-Way Sensitivity Analysis on the Impact to the ICER When Varying the Maintenance Cost of the Capnography Device, Adult Patients Undergoing Procedural Sedation



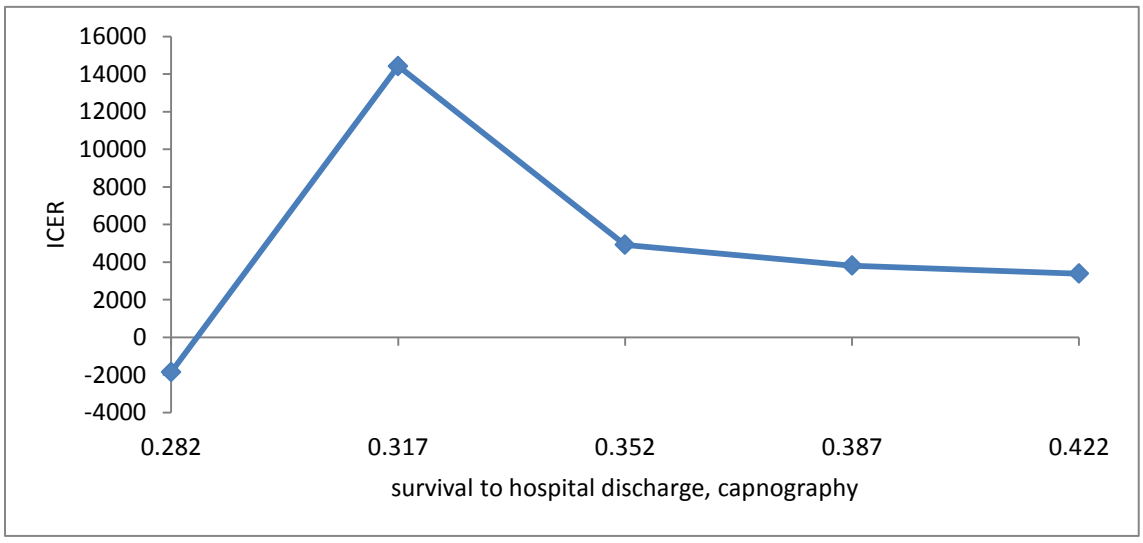
ICER = incremental cost-effectiveness ratio.

Figure 17: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Number of Patients a Device Serves Per Month, Adult Procedural Sedation



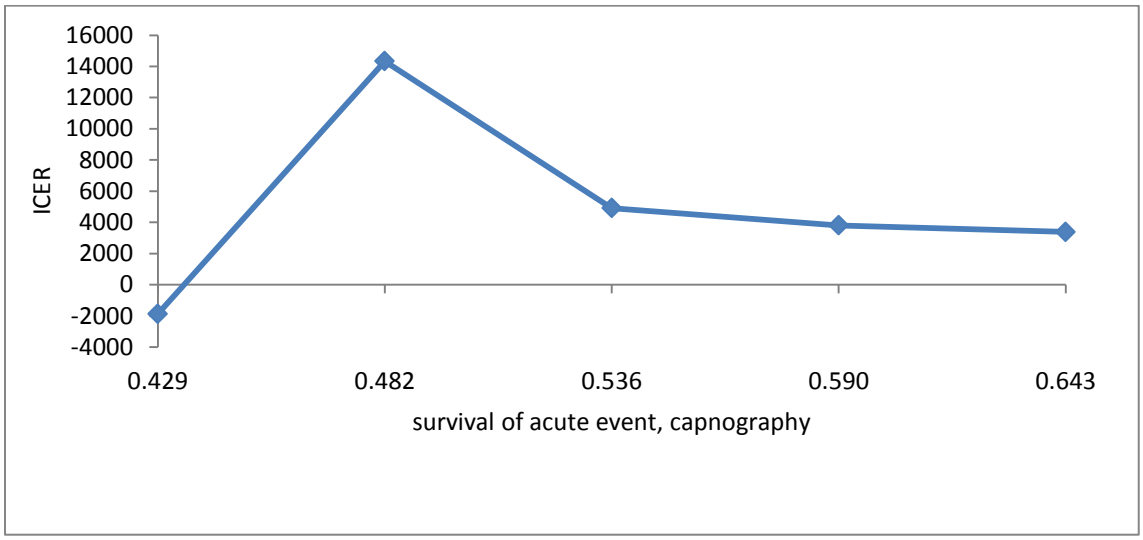
ICER = incremental cost-effectiveness ratio.

Figure 18: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Probability of Survival to Hospital Discharge for Patients Receiving Capnography, Adult Patients Undergoing CPR (Primary Model). Negative ICERs Represent Situation in Which Capnography With Standard Monitoring is Dominated by Standard Monitoring Alone



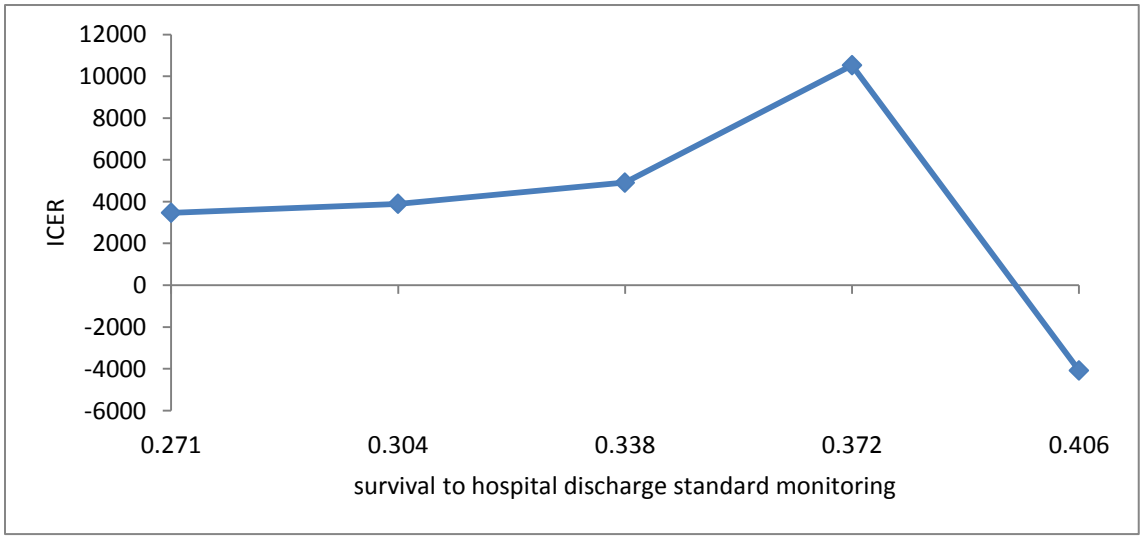
CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

Figure 19: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Survival Probability of Acute Event for Patients Receiving Capnography, Adult Patients Undergoing CPR (Primary Model). Negative ICERs Represent Situation in Which Capnography With Standard Monitoring is Dominated by Standard Monitoring Alone



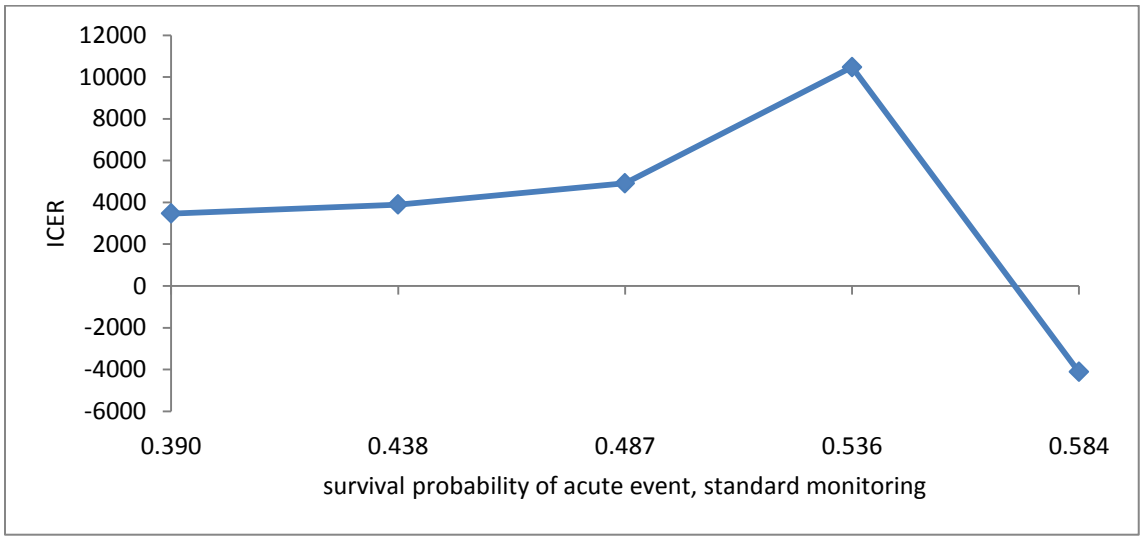
CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

Figure 20: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Probability of Survival to Hospital Discharge for Patients Receiving Standard Monitoring, Adult Patients Undergoing CPR (Primary Model). Negative ICERs Represent Situation in Which Capnography With Standard Monitoring is Dominated by Standard Monitoring Alone



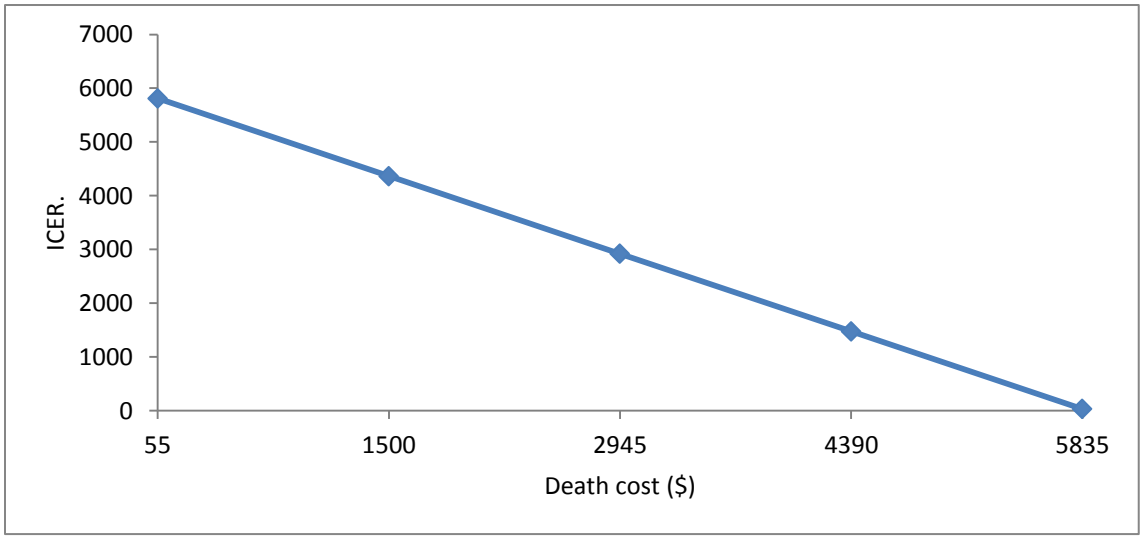
CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

Figure 21: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Survival Probability of Acute Event for Patients Receiving Standard Monitoring, Adult Patients Undergoing CPR (Primary Model). Negative ICERs Represent Situation in Which Capnography With Standard Monitoring is Dominated by Standard Monitoring Alone



CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

Figure 22: One-way Sensitivity Analysis on the Impact to the ICER When Varying the Cost of in-Hospital Death, Adult Patients Undergoing CPR (Primary Model). Negative ICERs Represent Situation in Which Capnography With Standard Monitoring is Dominated by Standard Monitoring Alone



CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

Table 88: Probabilistic Results When Varying Both the Baseline Rate of Respiratory Failure and RR of Respiratory Failure in Capnography and Standard Monitoring Compared With Standard Monitoring Alone, ICER (Cost per Respiratory Failure Averted)

RR	Rate		
	0.226	0.283	0.339
Adult patients undergoing procedural sedation			
0.59	385.70	280.64	211.82
0.67	494.36	363.83	278.34
0.75	672.57	500.27	387.42
0.83	1018.50	765.12	599.16

ICER = incremental cost-effectiveness ratio; RR = Relative risk of capnography versus standard monitoring.
Note: Rate — Respiratory failure rate of standard monitoring.

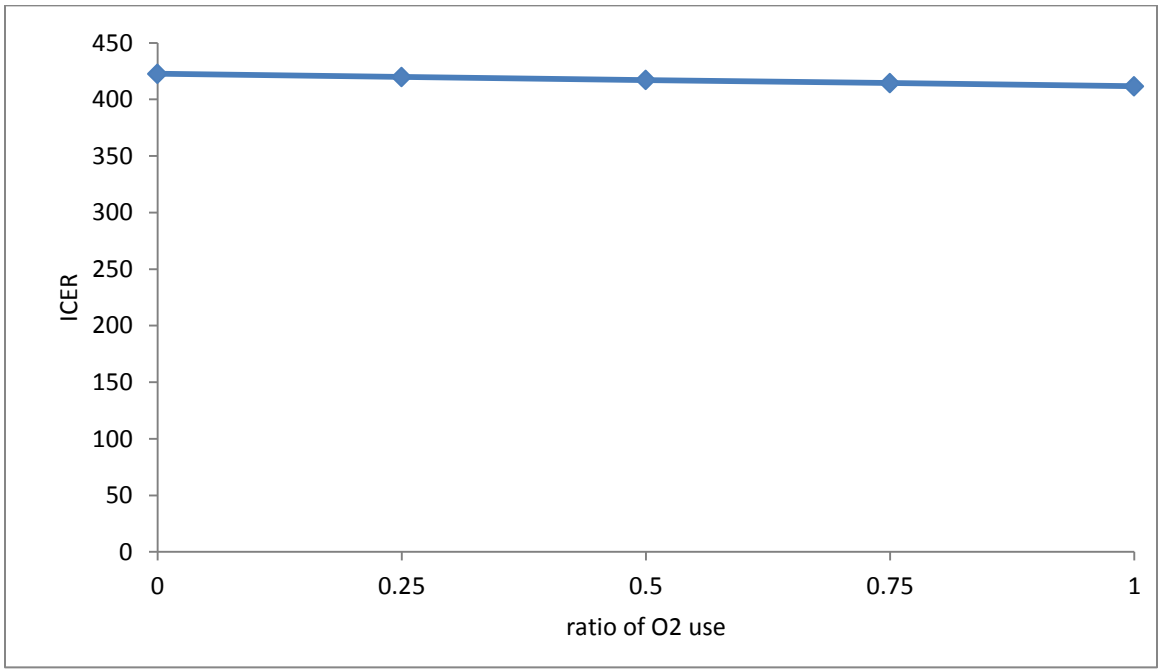
Table 89: Probabilistic Results When Varying Both the Number of Patients Served per Month and Price of Capnography, ICER (Cost per Averted Respiratory Failure for Sedation Group or Cost per Life Saved for CPR Group)

Price ($)	Number of patients served per month			
	4	23	42	60
Adult patients undergoing procedural sedation				
3,000	312.44	189.52	177.81	173.56
5,000	413.33	206.77	187.26	180.17
7,000	518.84	224.02	196.71	186.79
Adult patients undergoing CPR				
3,000	4,585.13	4,103.52	4,099.98	4,069.52
5,000	4,904.53	4,204.62	4,141.93	4,094.24
7,000	5,279.59	4,207.87	4,150.71	4,112.67

CPR = cardiopulmonary resuscitation; ICER = incremental cost-effectiveness ratio.

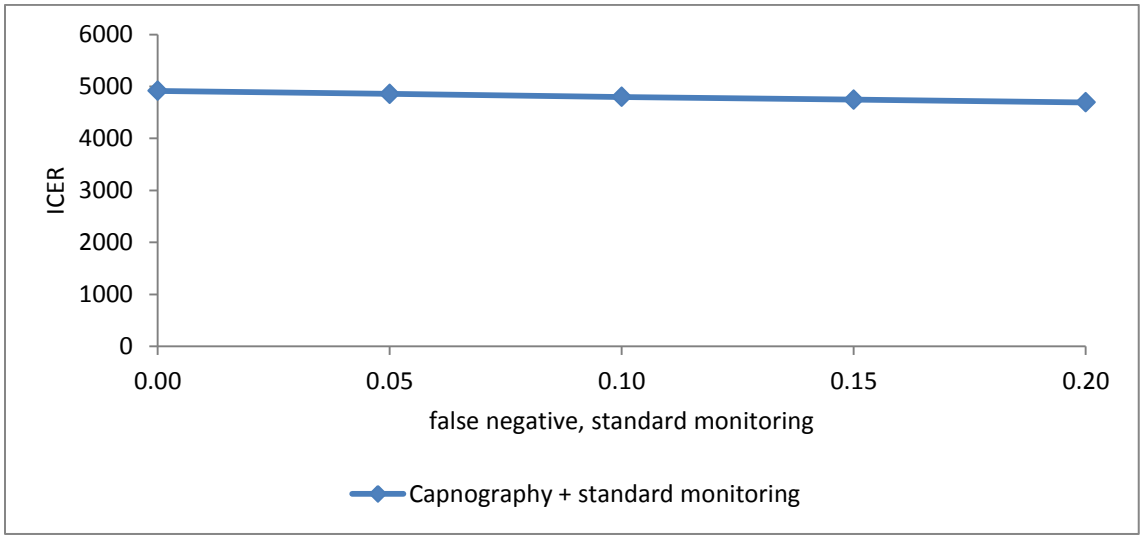
Figure 23: Structural Sensitivity Analysis to Evaluate the Relationship Between Ventilation Assistance and Supplemental Oxygen Use

Note: This figure highlights the extent to which the ICER is impacted when varying the ratio of patients receiving both ventilation assistance and supplemental O_2 use in adult patients undergoing procedural sedation.



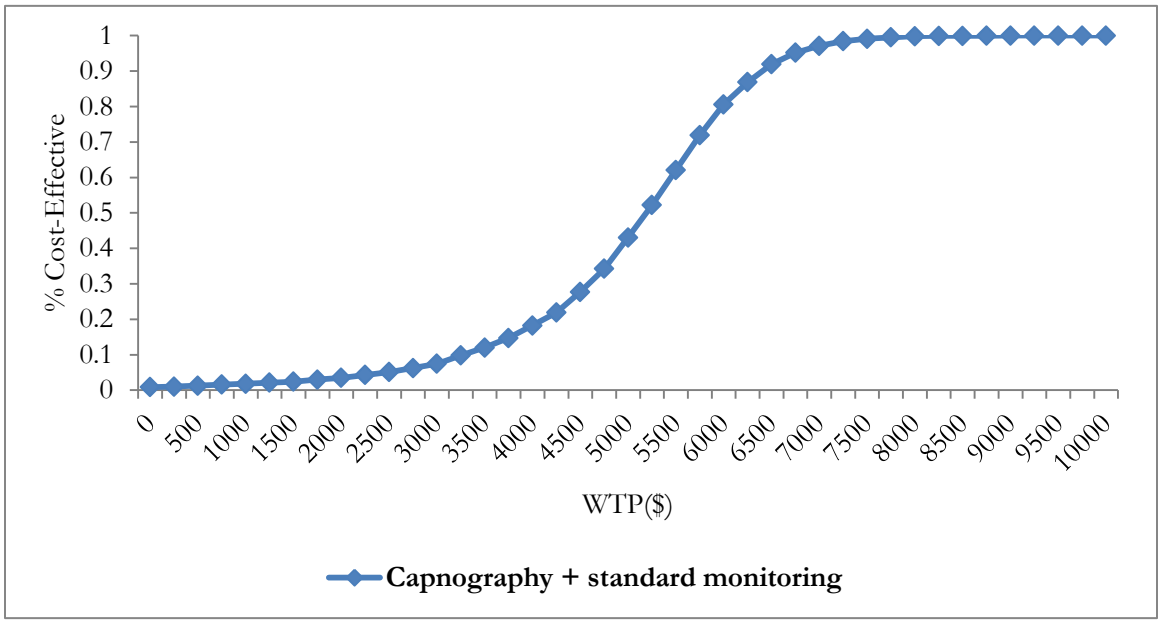
ICER = incremental cost-effectiveness ratio.

Figure 24: Structural Sensitivity Analysis Varying the Probability of Undetected ETT Misplacement in Patients Receiving Standard Monitoring, Adult Patients Undergoing CPR



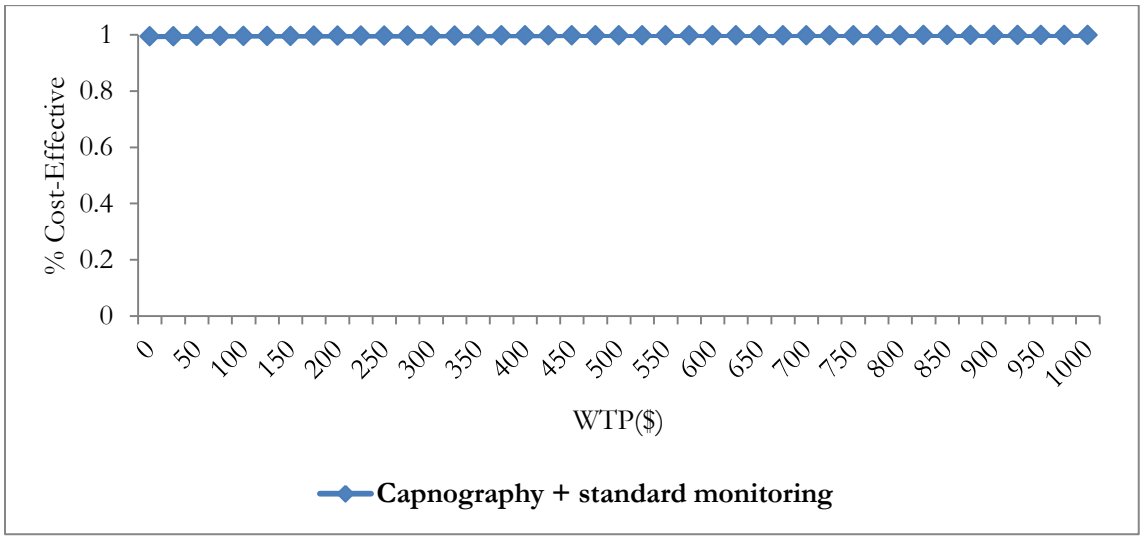
CPR = cardiopulmonary resuscitation; ETT = endotracheal tube; ICER = incremental cost-effectiveness ratio.

Figure 25: Cost-effectiveness Acceptability Curve of Capnography With Standard Monitoring, Adult Patients Undergoing CPR (Secondary Analysis — Using Data From Phelan et al.[83])



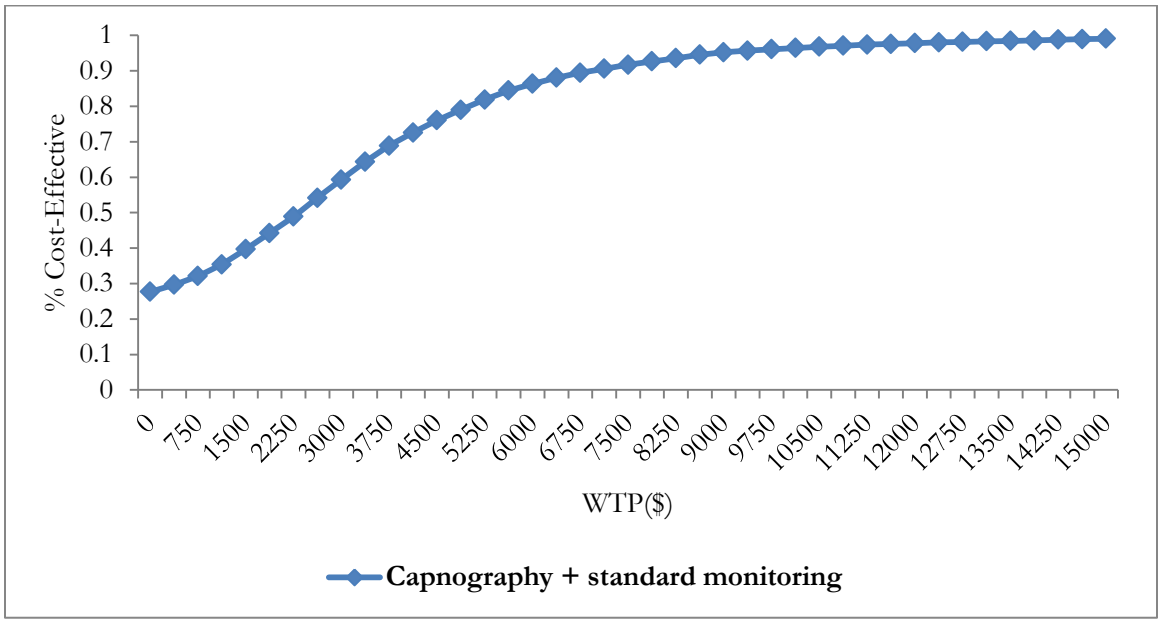
CPR = cardiopulmonary resuscitation; WTP = willingness to pay.

Figure 26: Cost-effectiveness Acceptability Curve of Capnography With Standard Monitoring, Adult Patients in Serious or Critical Condition (Exploratory Analysis)



WTP = willingness to pay.

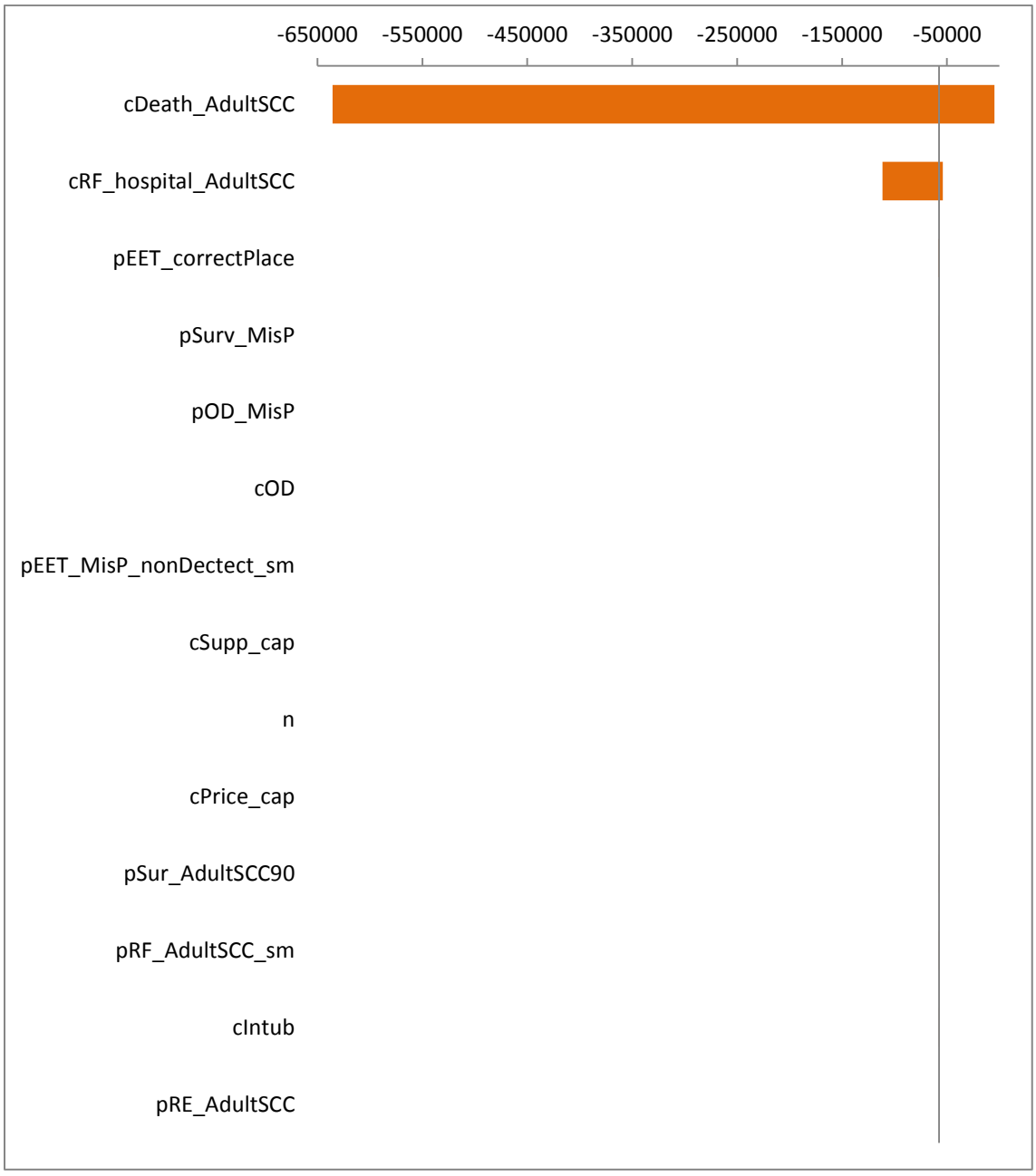
Figure 27: Cost-effectiveness Acceptability Curve of Capnography With Standard Monitoring, Adult Patients in Post-operative Care (Exploratory Analysis)



WTP = willingness to pay.

Figure 28: Tornado Diagram, Adult Patients in Serious and Critical Condition. Negative ICERs Represent Situation in Which Standard Monitoring is Dominated by Capnography.

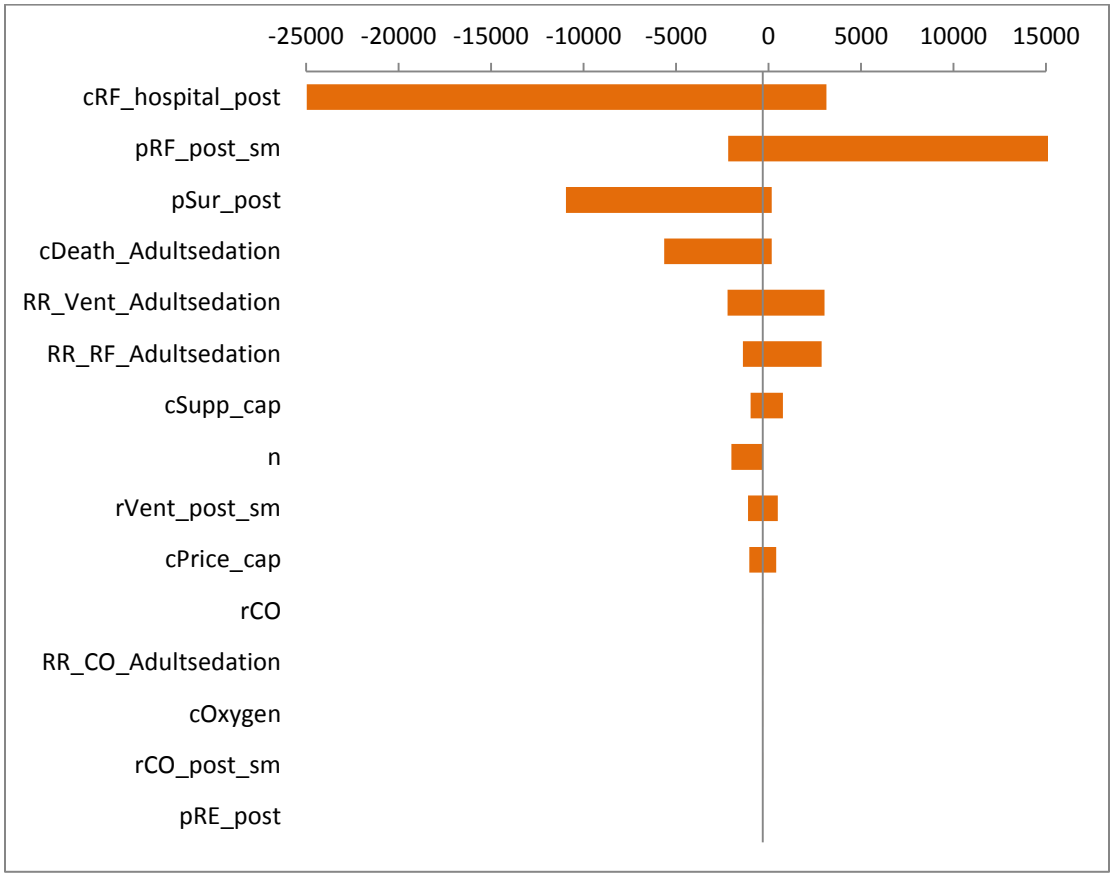
Note: See Table 87 in APPENDIX 13: Detailed Economic Results for a description of variables.



ICER = incremental cost-effectiveness ratio.

Figure 29: Tornado Diagram, Adults in Post-operative Care. Negative ICERs Represent Situation in Which Standard Monitoring is Dominated by Capnography.

Note: See Table 87 in APPENDIX 13: Detailed Economic Results for a description of variables.



ICER = incremental cost-effectiveness ratio.

Table 90: Results When Varying Both the Number of Patients Served per Month and Price of Capnography, Costs Difference (i.e., Capnography With Standard Monitoring — Standard Monitoring)

Price ($)	Number of patients served per month			
	4	**23**	**42**	**60**
Pediatric patients undergoing procedural sedation				
3000	40.00	29.69	28.71	28.33
5000	53.33	31.07	29.41	29.22
7000	56.66	32.64	30.26	29.44