Cost Analysis of Desflurane and Sevoflurane

An Integrative Review and Implementation Project

Introducing the Volatile Anesthetic Cost Calculator (iVAC©)

John K. Varkey, RN, BSN

john.varkey@tcu.edu

Capstone Project

DOCTOR OF NURSING PRACTICE

Project Chair: Mark Welliver, CRNA, DNP, ARNP
Advisor: Margaret Roseann Diehl, CRNA, DNP

Harris College of Nursing and Health Sciences
School of Nurse Anesthesia

Texas Christian University

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Abstract

**Background:** Sevoflurane and desflurane are the newest volatile anesthetic agents available. Compared to older agents they allow for faster induction and emergence from anesthesia. Their characteristic of quicker action is desirable. However there is some debate as to which volatile anesthetic agent, desflurane or sevoflurane, is more cost effective for anesthesia professionals to administer. Cost is a consideration when choosing between these two anesthetics.

**Methods:** A literature review was conducted evaluating various methods for comparing sevoflurane and desflurane utilization and cost. The key words “sevoflurane”, “desflurane”, “cost effectiveness”, “cost”, “pharmacoeconomics”, and “cost analysis” were used in various combinations to search EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, and ScienceDirect. Inclusion criteria were articles written in English and patients over 18 years of age. Each article was reviewed and chosen based on cost analysis of desflurane and sevoflurane.

**Results:** Seven methods of cost analysis were discovered in the literature: Dion’s formula, Loke’s formula, a volume percent equation, a four-compartment model, weight measurement, volume measurement, and minimum alveolar concentration comparison. It was determined that Dion’s formula is the more reliable method for anesthesia professionals to determine volatile anesthetic agent cost. The amount of vapor used determines cost, which makes Dion’s formula a reliable method in cost calculation. In order to determine total cost of sevoflurane or desflurane the acquisition cost, percent concentration, fresh gas flow rate, density, and molecular weight must be factored. There was, in general, an insignificant cost difference between desflurane and sevoflurane when using each volatile anesthetic agent at lowest allowable fresh gas flow rates.

**Conclusion:** The cost effectiveness differences between sevoflurane and desflurane varies depending on the acquisition cost and delivery technique. Anesthesia professionals can control the cost of volatile
anesthetic agents use through fresh gas flow rates. Low fresh gas flow delivery with modern anesthesia machines is most cost effective for both volatile anesthetic agents. The difference in utilization costs between sevoflurane and desflurane is minimal when respective low fresh gas flow rates are used.

PART ONE: Introduction and Overview

Introduction

Inhalational agents have been a mainstay in anesthesia prior to the creation of the hypodermic needle. Nitrous oxide, the world’s first inhalational agent, was synthesized in 1772 and is still in use today.\(^1\) By the late 1800s nitrous oxide, diethyl ether, and chloroform were administered by anesthesia professionals to facilitate surgery.\(^1\) Halogenated gases were created in the 1940s and were safer, more stable, and more potent anesthetic agents.\(^1\) In order to meet the growing needs for a rapid acting and dissipating anesthetic agent for surgery, lower solubility volatile anesthetic agents (VAAs) were created: isoflurane (1981), desflurane (1992), and sevoflurane (1995).\(^1\) Anesthesia professionals have better control of their anesthetic technique by using these lower solubility agents. The two newest and relatively more expensive agents, sevoflurane and desflurane, have many benefits including faster induction and emergence.\(^2\) Using sevoflurane or desflurane does increase the cost of anesthesia when compared to older VAAs, but is it preferable to choose one of these newer agent’s based on cost differences between the two? Determining the cost of VAAs is important to many institutions attempting to buffer the rising cost of healthcare by cost effective use of drugs and therapies.

Overview

This paper presents a cost analysis of desflurane and sevoflurane, and subsequently determines if there is any cost difference. An intervention is described for the development of an iApp for mobile devices, which may be utilized as a quick and accessible resource designed for use by anesthesia providers at any institution. The scientific rationale and implementation of this iApp will be reviewed.
Institutional Review Board

Approval from the Texas Christian University IRB was requested for this DNP Capstone Project. Approval from the IRB board was granted September 2012 as shown in Appendix 1.

Methodology

A database search of the literature was conducted beginning September 2010 through January 2012. The databases searched included EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, Google Scholar, and ScienceDirect using the key terms and phrases: Sevoflurane, desflurane, cost-effectiveness, cost, pharmacoconomics, and cost analysis. Inclusion criteria were patients over 18 years of age. Non-English language articles were excluded. Each article was reviewed and chosen based on cost analysis of desflurane and sevoflurane. Each article’s references were checked, cross checked, and those articles that fit the above criteria were also included. Evidence retrieved included randomized control trials, retrospective cohort studies, and expert opinion from 1997-2010. The compiled evidence provides insight regarding a reliable method of calculating volatile anesthetic cost and allows recommendations for anesthesia practice.

PART TWO: Literature

Background

Cost containment and cost effective use of resources has become a priority within healthcare. This has created a challenge for anesthesia providers wanting to deliver high quality healthcare that is safe yet economical. In anesthesia, volatile anesthetic agents may account for up to 20% of total anesthesia costs. Sevoflurane and desflurane are the two newest and relatively expensive VAAs used for anesthesia. Each agent has its own inherent distinct advantages. Sevoflurane is a potent bronchodilator that may be ideal for asthmatic patients and patients with reactive airways. Sevoflurane
is a versatile sweet smelling VAA that may be used for mask induction and maintenance of anesthesia. Desflurane has the lowest blood gas solubility of all VAAs, making it the preferential agent in the bariatric population and for short day surgery cases. Blood gas solubility, also known as the blood gas partition coefficient, “describes the partitioning of an anesthetic between blood and gas.” A lower blood gas solubility leads to less patient uptake, faster induction, and faster emergence. Both agents may be used safely in the inpatient and outpatient surgery settings in healthy or ill patient populations. The acquisition cost of sevoflurane and desflurane varies per institution, location, and contract. A difficult challenge for hospital pharmacies is budgeting drug cost. Budgeting for intravenous drugs is much simpler than VAA since there is a direct relationship between the amount of drug acquired and administered. Calculating VAA drug cost is made obscure by the delivery method. VAAs are purchased in liquid form and administered through a vaporizer, making it difficult to directly measure how much VAA is used per case without the aid of a vapor analyzer. Varying delivery concentrations and delivery techniques may increase or decrease total consumption of VAAs and significantly change acquisition costs.

**Review of Literature**

A thorough search of the literature yielded eleven articles that calculated the cost of administering VAA. Ten of these articles directly compared the cost of administering sevoflurane and desflurane. Two of the articles were from randomized control trials (RCTs). Seven methods were used to determine cost of VAA: A precision weighing system, a computer data log, minimum alveolar concentration (MAC), a four compartment model, a volume percent formula, Dion’s formula, and Loke’s formula. Seven articles favored sevoflurane (Table 1) as more cost effective when comparing similar flow rates, two articles favored desflurane (Table 2), and one article found no significant cost difference between inhalation groups (Table 3). Each article was rated according to the Level of Evidence Table (Appendix 2) and ratings may be found in Tables 1, 2, and 3.
Precision Weighing System

Boldt et al performed a randomized control trial (RCT) in 1998 comparing standard and new anesthetic techniques with cost. Eighty patients undergoing laparoscopic cholecystectomy or a subtotal thyroidectomy were randomly divided into four groups. Group 1 received propofol and sufentanil, Group 2 received desflurane and sufentanil, Group 3 received sevoflurane and sufentanil, and Group 4 received isoflurane and sufentanil for anesthesia. A fresh gas flow (FGF) of 1.5-2 L/min of oxygen and 60% nitrous oxide were used during maintenance. The average end tidal concentration of sevoflurane ranged from 1.1% to 2.5% and end tidal concentration of desflurane ranged from 3.5% to 7.2%. The authors were skeptical about the use of formulas and resorted to weighing vapors using a precision weighing machine. Volatile anesthetic consumption was measured by weighing vaporizers after each case using a precision weighing machine. Each agent was measured to the nearest 0.1 g and subsequently converted to mL (sevoflurane 1.52 g/mL, desflurane 1.465 g/mL). The authors found no significant difference between the cost of using sevoflurane or desflurane. The authors oppose the use of formula to determine VAA cost because anesthesia is not administered using formula and since anesthesia flow rates are constantly adjusted throughout a case. According to the authors, the use of precision weighing machines allow for precise measurement of consumed liquid quantity. Boldt et al stated that reduction of FGF, regardless of VAA, results in considerable volatile anesthetic savings. Theoretically the authors propose desflurane as more economical than sevoflurane at low flow rates because equilibration occurs more rapidly. There was no significant difference in the cost of administering isoflurane, desflurane, or sevoflurane.

Computer Data Log

Cobos et al at the University of Nebraska Medical Center in 2007 used a computer to log FGF and inhaled concentrations of anesthetics every minute during 47 cases. The authors stated that...
sevoflurane FGF, MAC equivalents, and cost per minute were higher than desflurane at their institution. FGF for sevoflurane was 3.4 L/min and desflurane was 2.1 L/min, and cost per minute of sevoflurane was $0.79 and desflurane was $0.56. The authors did not mention how they determined cost of each VAA and there was a discrepancy in their data. The MAC equivalents listed for sevoflurane is lower than desflurane at 0.90 and 1.12 respectively. The research abstract was available online through the American Society of Anesthesiologist (ASA) website. The abstract did not define MAC equivalent. The authors proposed that reducing FGF by half may theoretically decrease the cost of all VAAs by half. Attempts to reach the author were unsuccessful.

Minimum Alveolar Concentration

At Montefiore Medical Center in 2009 the pharmacy manager, Frank Aroh, decided to remove desflurane from all operating rooms (OR) in an effort to reduce cost. He claimed that although sevoflurane is more expensive per unit than desflurane, it takes three bottles of desflurane to produce the anesthesia of one bottle of sevoflurane. It can be inferred that this is in reference to the MAC of each agent, which is not explicitly stated. Dr. Eger in an editorial in 2010 stated that, although the unit cost of sevoflurane was more expensive than desflurane, it would take roughly three times the amount of desflurane to create a comparable anesthetic depth at a given flow rate. This is due to their differences in potency, since approximately 2% of sevoflurane and 6% of desflurane is needed to create one MAC. MAC is defined as the minimum alveolar concentration of an inhaled anesthetic agent that produces immobility in 50% of the population exposed to a surgical incision. Mr. Aroh claimed that although sevoflurane was more expensive per mL, the MAC for desflurane was three times the MAC for sevoflurane, thus making sevoflurane the cheaper agent to administer. Mr. Aroh based his calculations on only two variables, MAC and unit cost. Mr. Aroh claims that Montefiore Medical Center was able to save $100,000 over one year by increasing sevoflurane usage while simultaneously decreasing
desflurane usage.⁸ No method for calculating cost or VAA consumption were mentioned and no cost analysis was made.

Four Compartment Model

Lockwood and White in 2001 incorporated the Weiskopf and Eger four compartment model to create a computer model to compare direct cost of isoflurane, desflurane, and sevoflurane in open and closed systems.¹² The four-compartment computer model takes into consideration the solubility, absorption, and elimination of an anesthetic agent in the body.¹² The initial study by Weiskopf and Eger compared isoflurane and desflurane which varied significantly in their solubility in blood.¹² Lockwood and White took Weiskopf and Eger’s methods and compared isoflurane, desflurane, and sevoflurane. They used patient data in a closed system and compared it to a computer model.¹² In the first part of their discussion, they predict ratio of liquid anesthetic used at FGF of 4, 2, 1, and 0.2 L/min.¹² The authors used their data to create ratio of liquid anesthetic used, comparing desflurane to sevoflurane however they did not mention the acquisition cost or formula they used to determine cost. Lockwood and White concluded that the ratios of usage shown are invariable and can always be used to determine relative expense.¹² Lockwood and White found in an open system the cost of desflurane and sevoflurane are approximately the same, but in a closed system desflurane is slightly less expensive than sevoflurane.¹²

Vaporizer Dial Setting

Puckett and Andrews in 1997 calculated the cost of sevoflurane, desflurane, and isoflurane using a volume percent equation and dialed settings.¹⁴ The volume percent equation was used to calculate the amount of vapor produced at 1 MAC and FGF 2 L/min.¹⁴ The vapor produced by one mL of VAA was calculated using the mL of vapor per mL liquid equation. The authors were then able to convert the amount of vapor into mL of VAA, and then they used the cost per mL to determine cost per hour. The
authors assumed that the vaporizer dial setting accurately denotes the concentration of vapor being delivered. The authors did not establish calibration of the vaporizers pre-measurement nor confirmed accurate delivery output. They compared the cost of sevoflurane and desflurane at the same flow rate and found sevoflurane to be slightly less expensive.\textsuperscript{14}

Dion’s Formula

The cost of a VAA may be determined using the market price, potency, amount of vapor produced, and the fresh gas flow rate.\textsuperscript{3} In 1992 in a letter to the editor Dr. Peter Dion stated a formula for directly measuring the cost of inhaled anesthetic incorporating ideal gas law.\textsuperscript{15} The cost of an anesthetic agent can be calculated from the concentration (\%) of gas delivered, FGF (L/min), duration of inhaled anesthetic delivery (min), molecular weight (MW in g), cost per mL (in dollars), a factor 2412 to account for the molar volume of a gas at 21 °C (24.12 L), and density (D in g/mL).\textsuperscript{15} The formula is as follows:

$$\text{Cost ($)} = \frac{[(\text{Concentration})(\text{FGF})(\text{Duration})(\text{MW})(\text{Cost/mL})]}{[(2412)(\text{D})]}$$

Dion’s formula incorporates ideal gas law in order to convert mL VAA vapor into mL of VAA liquid, which is then used to determine cost using the acquisition price per mL. In order to convert volume of vapor into an mL of VAA, the density and molecular weight are used to convert the VAA vapor into moles, and moles are subsequently converted into mL of liquid VAA using a conversion factor of 2412. According to the universal gas law equation, one mole of an ideal gas at one atmosphere pressure and corresponding to 21°C will liberate 24.12 liters of vapor.\textsuperscript{15}

Dion’s formula does not take into account patient specific uptake and distribution but rather amount of delivered inhaled agent. The amount of vapor used determines cost, which makes Dion’s
formula a reliable method in cost calculation. Five studies were found in the literature search using Dion’s formula, and all five supported sevoflurane as a more economical inhalation agent than desflurane. See Table 1 for studies supporting the use of sevoflurane.

Jellish et al performed a RCT in 2005 comparing desflurane and sevoflurane for middle ear microsurgery.\textsuperscript{16} One hundred healthy adult patients were randomly divided into two groups. Group 1 received desflurane with an end tidal concentration between 6-9% and Group 2 received sevoflurane with an end tidal concentration between 2-3%.\textsuperscript{16} Both groups used similar FGF of 2-3 L/min with a 50% oxygen/air mixture.\textsuperscript{16} The authors used the Dion Formula to calculate cost for each case and determined that desflurane was five dollars more expensive per case than sevoflurane.\textsuperscript{16} The authors acknowledged that the FGF used for desflurane may be higher than those typically used in desflurane anesthesia.\textsuperscript{16} The cost comparison for sevoflurane and desflurane was made at similar flow rates.

Weinberg et al performed an 11-year retrospective analysis on the pharmacoeconomics of VAA in Australia between 1997 and 2007.\textsuperscript{17} While the patient case load for this single center study increased 11%, the cumulative cost of isoflurane, desflurane, and sevoflurane increased 168%.\textsuperscript{17} In Australian dollars, the cost of isoflurane decreased from $157 per 250mL bottle in 1997 to $109 in 2007.\textsuperscript{17} This is parallel to the number of bottles if isoflurane used, as isoflurane use decreased from 384 bottles in 1997 to 204 bottles in 2007.\textsuperscript{17} During this same time period, sevoflurane cost decreased slightly from $336 per 250mL bottle in 1997 to $265 in 2007 while the number of sevoflurane bottles increased from 226 bottles to 875 bottles over the same time period.\textsuperscript{17} Desflurane was introduced in 2002 and its cost per 240mL bottle increased from $170 to $180 while the number of bottles used increased from 34 bottles to 163 bottles.\textsuperscript{16} The authors used Dion’s formula to calculate cost per hour of isoflurane, desflurane, and sevoflurane at various flow rates. Using Dion’s formula the authors found that isoflurane was the cheapest agent to administer followed by sevoflurane and desflurane.\textsuperscript{17} The authors concluded that the
shift from isoflurane to the more expensive sevoflurane and desflurane was the reason for the increase in overall VAA cost. The authors did not determine if sevoflurane or desflurane was cheaper to administer but they did include a cost per hour for each VAA at variable flow rates. When comparing similar flow rates, sevoflurane was the cheaper agent. When comparing variable flow rates, the cost of administering sevoflurane at 1 Liter/min ($6.94) was similar to desflurane at 0.5 L/min ($6.42). When using the manufacturer’s recommendation for prolonged procedures, sevoflurane at FGF of 2 L/min was significantly more expensive ($13.88) than desflurane at 0.5 L/min ($6.42). All values are in Australian dollars.

Golembiewski in 2010 used Dion’s formula to compare wholesale cost of sevoflurane and desflurane at FGF 1-3 L/min. The author determined the anesthetist controlled cost of VAA by the FGF. The amount of anesthetic agent wasted is also directly correlated to the FGF. The FGF may vary according to VAA being used, intraoperative conditions, and anesthetist. Sevoflurane was cheaper than desflurane to administer when comparing similar flow rates. Golembiewski also compared the cost per MAC hour at different flow rates and determined that the cost of administering desflurane at FGF 1 L/min was similar to the FGF of sevoflurane at 2 L/min (Table 1). The author recommends analyzing anesthesia records to assess patterns in provider use of VAA, concentration, and FGF. The use of low flow anesthesia for all VAAs decreases overall cost while maximizing rebreathing.

Chernin in 2004 described the cost minimization analysis of inhaled agents at Sarasota Memorial Hospital. The acquisition cost of sevoflurane was much higher than desflurane, $0.83/mL and $0.41/mL respectively. Despite the higher acquisition cost of sevoflurane, the cost of administering
Desflurane per MAC hour was higher than sevoflurane at similar flow rates. Dion’s formula was used to calculate cost but the FGF used in the study and MAC values were not disclosed. By using the data supplied and Dion’s formula and assuming a MAC of 2% for sevoflurane and 6% for desflurane, it was determined the author used FGF of 1 L/min, 2 L/min, and 3 L/min for comparison. At similar flow rates sevoflurane was cheaper to administer than desflurane. When comparing lowest allowable flow rates, the cost of administering desflurane at 0.5 L/min is more cost effective than administering sevoflurane at 1 L/min or higher. The author identifies four interventions that may help reduce VAA cost: establishing a fast-track recovery protocol, using low FGF, monitoring vaporizer settings, and providing feedback to anesthesiologists.19

Dr. Lubarsky, Vigoda, and Wagner, in conjunction with Abbott, distributed an article in Formulary on October 2007 discussing economic and safety considerations of desflurane and sevoflurane.20 The authors claim that at FGF 0.5-1 L/min sevoflurane and desflurane provide the same level of control of depth of anesthesia as older agents at FGF 2-4 L/min.20 The author’s claim the primary differences between sevoflurane and desflurane are blood and tissue solubility and potency. The acquisition cost for brand sevoflurane (Ultane) was more expensive than desflurane (Table 1) but the calculated MAC hour cost was less expensive for brand sevoflurane. The authors claimed to use Dion’s formula to calculate MAC hour cost but failed to disclose the concentration they used for 1 MAC and FGF. MAC-hour cost may vary depending on the FGF used to calculate cost. Sevoflurane has FGF limits while desflurane has no restrictions on FGF. Also, a discrepancy was noted in the use of Dion’s formula. The molar volume of gas is listed as 2412 liters in the article, but the 2412 in Dion’s formula represents 24.12 liters. This publication was supported by an educational grant from Abbott, the company that manufactures Ultane, and does contain bias towards brand sevoflurane. The author claims brand sevoflurane is the most economical agent based on MAC-hour but fails to incorporate differences in FGF. Abbott does not manufacture desflurane.
Loke’s Formula

Loke and Shearer, in a letter to the editor in 1993, questioned the use of Dion’s formula in newer volatile agents. They used Dion’s original formula and incorporated ideal gas directly law into the formula rather than using a conversion factor of 2412 for 24.12 Liters, which represents molar volume of gas at one atmosphere at 21°C.

For comparison purposes,

Dion’s Formula

Cost per MAC hour ($) = \frac{[(\text{MAC})(\text{FGF})(60\text{min})(\text{MW})(\text{Cost/mL})]}{[(2412)(D)]}

Loke’s Formula

Cost per MAC hour ($) = \frac{[(\text{MAC})(\text{FGF})(60\text{min})(\text{MW})(\text{Cost/mL})]}{[(\text{Pressure}/(\text{RT})(D))]}

These formulas are similar; however with Loke’s formula the user would substitute the atmospheric temperature in Pascals, the ideal gas law constant 8.314, and temperature in Kelvin for the constant 2412. Loke and Shearer also included the cost of carrier gases nitrous oxide and oxygen and compared Halothane, Enflurane, and Isoflurane. At the time of this publication desflurane and sevoflurane were unavailable in Australia.

Synthesis

Determining cost of VAA is a difficult task, made even more challenging by the various methods available to determine cost. Of the seven methods discovered in the literature, six were found to be either impractical or inaccurate. Weighing vapors is impossible to replicate in a busy operating room setting. The computer data log method and four compartment model methods do not disclose cost calculation, making it difficult to determine accuracy. A simple comparison of MAC does not factor in
important variables such as FGF and differences in VAA properties. Using the volume percent calculation is inaccurate since it is based on a dialed concentration and not an actual concentration determined by a gas analyzer.\textsuperscript{14} Loke’s formula, a modified version of Dion’s formula, includes the atmospheric pressure and temperature in addition to other variables in Dion’s formula.\textsuperscript{21} In reality, a cost comparison would occur at the same facility and the atmospheric pressure and temperature would remain constant, rendering the use of Loke’s formula unnecessary. Dion’s formula was determined to be easily reproducible, accurate, and is the most referenced method for calculating cost in the literature. Weinberg et al stated, “this method is a simple pharmacoeconomic tool that can be used by every anesthetist.”\textsuperscript{17} Therefore, Dion’s method was utilized in the creation of a resource iApp tool.

The majority of the literature supports sevoflurane\textsuperscript{8,14,16,17,18,19,20} as the most cost effective agent using similar flow rates. Several articles\textsuperscript{6,7,16,17,18,19} advocate the use of low flow gas rates, however only one\textsuperscript{18} makes a case for comparing each agent at lowest allowable flow rates. Currently in the United States the FDA recommends FGF no less than 1 L/min for cases less than 2 MAC hours and FGF 2 L/min for cases longer than 2 MAC hours for sevoflurane.\textsuperscript{22} Desflurane has no restrictions on flow rate and may be administered with FGF as low as 0.5 L/min. The comparison of sevoflurane and desflurane at lowest allowable flow rates is the most accurate method in determining true cost. Two of the seven studies that favored sevoflurane as cost effective with similar flow rates favored desflurane as the more cost effective agent when lowest allowable FGF were compared using FDA recommendations for cases less than two MAC hours (Table 4), and three studies favored desflurane when comparing cases longer than 2 MAC hours (Table 5).

Conclusions that one drug is more or less cost effective than another can rarely be translated from one region to another because of the variability in drug acquisition cost and availability of generic formulations of sevoflurane. Therefore in some institutions sevoflurane may be less expensive than
desflurane and in others the opposite may hold true. In accordance with Dion’s formula, anesthesia professionals are able to decrease cost of any VAA agent by using low FGF.

Part THREE: Intervention

Using Dion’s formula, a cost comparison was made using current acquisition prices in California and in Florida. Also, the formulation of an iApp for cellular phones using Dion’s formula was proposed. The iApp incorporates Dion’s formula derived from ideal gas law. It is a tool healthcare providers may use to calculate cost. This iApp may dispel misconceptions regarding the perceived cost of VAAs and prove the cost savings advantage of using low flow anesthesia.

Advantages of Low Flow Anesthesia

Desflurane and sevoflurane have low blood gas solubility coefficients that make them ideal for use with low flow anesthesia. Through the use of these insoluble agents the anesthetist is able to maintain tight control of the anesthetic depth. The low solubility permits rapid changes in the depth of anesthesia and also provides a greater economy at low FGF rates. Up to 90% of the administered dose of inhaled anesthetic escapes unused into the atmosphere. Low-flow anesthesia allows rebreathing, which conserves the amount of VAA used. Low-flow anesthesia also conserves patient’s body temperature, maintains inspired humidity, and minimizes environmental pollution. The anesthetist primarily controls the immediate cost of the inhaled agent through control of the FGF rate.

Disadvantages of Low Flow Anesthesia

Anesthesia professionals choose not to incorporate low flow anesthesia because of fears related to unsubstantiated anesthetic complications. These fears include difficulty controlling depth of anesthesia, accidental hypoxic events, hypercapnea, and the potential for toxic trace gases. The newer VAAs sevoflurane and desflurane have low blood gas solubilities which makes them easier for anesthesia
providers to titrate and maintain an adequate depth of anesthesia. Fears related to hypoxia and hypercapnea are mitigated with the use of gas analyzers and pulse oximetry. With low flow anesthesia the anesthesia provider must remain vigilant and monitor the patient’s hemodynamics closely. Low flow anesthesia is not recommended when gas must enter and leave a patient’s body quickly, as in induction and emergence. During induction it is common practice in anesthesia to use the concentration effect of high FGF and high VAA percent concentration to quickly reach an adequate anesthetic state in preparation for surgical stimulation. On emergence at the end of surgery high FGF are commonly used to quickly remove the VAA from the patient in order to return consciousness and transfer the patient to the recovery room.

Uptake and Distribution

When considering low flow anesthesia there must be a fundamental understanding of uptake and distribution of VAAs in order to appropriately adjust FGF and VAA concentration settings. When a VAA is administered the anesthetic affect related to brain concentration achieved is relative to the VAA concentration in the alveoli of the lungs. Older VAAs are more soluble in blood and therefore they take longer to diffuse into the brain. When an older VAA is administered, its higher blood solubility leads to a larger volume being absorbed by the blood. This blood uptake decreases the VAA concentration gradient between the alveoli and the blood. A smaller concentration gradient makes older VAAs more difficult to titrate and achieve an appropriate anesthetic state. With older VAAs, high FGF coupled with high alveolar concentration forces VAA uptake by the blood that will ultimately be diffused into the brain.

The newer less blood soluble VAAs (sevoflurane and desflurane) have a faster rise of the alveolar % concentration (FA) to inspired % concentration (FI) ratio because blood does not readily absorb them. Therefore, a quick rise in the alveolar concentration will have the effect of forcing VAA
into the blood by a concentration gradient that is quickly reversed upon blood circulation to the brain. Since sevoflurane and desflurane are relatively insoluble, they do not easily remain dissolved in blood and they will quickly diffuse into the brain. Continued VAA uptake occurs into four different tissue compartments: vessel rich group (VRG), muscle group, fat group and vessel poor group (VPG). Of these, the group with the highest cardiac output and highest anesthetic uptake is the VRG, which includes the brain and vital organs. The uptake by the vessel rich group is faster than the other three groups and is complete in approximately 5-10 minutes. After this initial time period, the uptake decreases and the alveolar concentration of gas remains relatively constant. At this point, the FGF may be lowered to a maintenance rate (low FGF) while the delivered VAA concentration will remain increased. Low FGF rates allow rebreathing of exhaled gases and rebreathed gas is partially depleted of VAA. In most anesthetic cases, it is this period of maintenance that constitutes the largest duration of the case. Therefore, the cost effectiveness of low FGF is dominant.

Compound A

Unlike desflurane, there are limitations to applying low flow anesthesia to sevoflurane. Sevoflurane is degraded to Compound A upon contact with carbon dioxide absorbents. Compound A is vinyl ether that has been known to cause nephrotoxicity in animals. Low flow anesthesia in closed circuits, warm CO₂ absorbents, and very dry CO₂ absorbents all enhance the production of Compound A. There have been no reported adverse renal effects from low-flow sevoflurane anesthesia however prolonged exposure to Compound A has the potential to cause proteinuria and glycosuria. The FDA recommends flow rates 1 to <2 L/min to not exceed 2 MAC-hours. Administering sevoflurane at FGF < 1 L/min are not recommended.
PART 4: Implementation and Results

The AHRQ Knowledge Transfer Model

The AHRQ knowledge transfer model was the framework used to implement this intervention of cost calculation and cost effective use of VAAs. (See figure 1) This framework was chosen since the model employs traditional approaches along with proactive partnerships to effectively bridge the gap between new knowledge and health care practitioners. This framework was chosen since the model employs traditional approaches along with proactive partnerships to effectively bridge the gap between new knowledge and health care practitioners.

The first stage of the model is knowledge creation and distillation. This process involves sifting through new knowledge to identify findings that are appropriate for healthcare providers. This was previously completed in a synthesis of the literature and the intervention is mentioned above.

The second stage of the AHRQ model identifies methods of diffusion and dissemination of new knowledge. This step involves creating partnerships with knowledge brokers and connector organizations to disseminate information through mass diffusion and targeted dissemination. Partnerships with knowledge broker organizations such as peer-reviewed journals will be sought. The plan includes the creation of a software application or iApp for cell phones to assist anesthesia professionals with quickly calculating VAA cost in the clinical setting.

The last phase of the AHRQ knowledge transfer process is known as implementation, end user adoption, and institutionalization. The goal of this phase is adoption and consistent use of research findings by healthcare providers. The intervention must provide incentives for the healthcare provider and the institution for adoption of the new practice. The iApp will be distributed for free and allow anyone to calculate cost quickly and efficiently. The provider would also be able to compare the cost of different VAAs, allowing the provider to make the most cost effective choice for a specific patient and surgery.
An iApp was created by John Varkey, RNA in conjunction with Dr. Mark Welliver, CRNA, and Tomin Kozhimala. It is named the CRNA iVAC™ and will be uploaded to the Apple iTunes store and be available to download and use.

**Results**

The variability in cost across regions and FGF is evident in the following example. A cost comparison of sevoflurane and desflurane was made with Dion’s formula using current acquisition prices from California and Florida (the particular institution names are withheld).

In California, the cost of sevoflurane is $0.38/mL and the cost of desflurane is $0.61/mL (known to author). Using Dion’s formula, a comparison was made at lowest allowable flow rates for cases less...
than 2 MAC hours. For cases less than two MAC hours, sevoflurane is cheaper to administer than desflurane at lowest allowable flow rates.

<table>
<thead>
<tr>
<th>VAA</th>
<th>MAC %</th>
<th>FGF</th>
<th>cost/bottle</th>
<th>mL/bottle</th>
<th>cost/mL</th>
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<td>$0.09</td>
<td>$5.30</td>
</tr>
</tbody>
</table>

For cases **longer than** 2 MAC hours, FGF for sevoflurane must be increased from 1 L/min to 2 L/min. In this example, sevoflurane is still slightly less expensive to administer than desflurane.

<table>
<thead>
<tr>
<th>VAA</th>
<th>MAC %</th>
<th>FGF</th>
<th>cost/bottle</th>
<th>mL/bottle</th>
<th>cost/mL</th>
<th>cost/min</th>
<th>Cost/MAC hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevo</td>
<td>2%</td>
<td>2 L/min</td>
<td>$93.93</td>
<td>250</td>
<td>$0.38</td>
<td>$0.08</td>
<td>$4.92</td>
</tr>
<tr>
<td>Des</td>
<td>6%</td>
<td>0.5 L/min</td>
<td>$147.00</td>
<td>240</td>
<td>$0.61</td>
<td>$0.09</td>
<td>$5.30</td>
</tr>
</tbody>
</table>

In Florida, the cost of sevoflurane is $0.64/mL and the cost of desflurane is $0.55/mL (known to author). Using Dion’s formula, a comparison was made at lowest allowable flow rates for cases less than 2 MAC hours. For cases **less than** two MAC hours, sevoflurane is cheaper to administer than desflurane at lowest allowable flow rates.

<table>
<thead>
<tr>
<th>VAA</th>
<th>MAC %</th>
<th>FGF</th>
<th>cost/bottle</th>
<th>mL/bottle</th>
<th>cost/mL</th>
<th>cost/min</th>
<th>Cost/MAC hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevo</td>
<td>2%</td>
<td>1 L/min</td>
<td>$159.50</td>
<td>250</td>
<td>$0.64</td>
<td>$0.07</td>
<td>$4.18</td>
</tr>
<tr>
<td>Des</td>
<td>6%</td>
<td>0.5 L/min</td>
<td>$133.00</td>
<td>240</td>
<td>$0.55</td>
<td>$0.08</td>
<td>$4.79</td>
</tr>
</tbody>
</table>
For cases longer than 2 MAC hours, FGF for sevoflurane must be increased from 1 L/min to 2 L/min. In this example, sevoflurane is significantly more expensive to administer than desflurane.

<table>
<thead>
<tr>
<th>VAA</th>
<th>MAC %</th>
<th>FGF</th>
<th>cost/bottle</th>
<th>mL/bottle</th>
<th>cost/mL</th>
<th>cost/min</th>
<th>Cost/MAC hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevo</td>
<td>2%</td>
<td>2 L/min</td>
<td>$159.50</td>
<td>250</td>
<td>$0.64</td>
<td>$0.14</td>
<td>$8.35</td>
</tr>
<tr>
<td>Des</td>
<td>6%</td>
<td>0.5 L/min</td>
<td>$133.00</td>
<td>240</td>
<td>$0.55</td>
<td>$0.08</td>
<td>$4.79</td>
</tr>
</tbody>
</table>

Part FIVE: Evaluation and Implications

Evaluation

The current literature supports the use of low flow anesthesia, regardless of VAA, in reducing anesthetic cost. The iApp created using Dion’s formula, named CRNA iVAC®, will be made available through TCU’s website at [http://www.crna.tcu.edu/dnp_capstone_projects.asp](http://www.crna.tcu.edu/dnp_capstone_projects.asp). The CRNA iVAC® will also be made available to download on iTunes. Feedback obtained from end users through the email address CRNAiVAC@gmail.com will be used to evaluate and upgrade effectiveness of the CRNA iVAC®.

Lessons Learned

This project determined cost of administering sevoflurane and desflurane but did not factor in additional cost of soda lime, carrier gases, opioids, antiemetics, and recovery time. The cost for the TEC 6 Desflurane vaporizer was also not factored into the overall cost of VAA. Some older anesthesia machines may not be able to compensate for lower FGF. Low FGF should only be used in the presence of standard monitoring equipment including a gas analyzer, end tidal CO₂ monitor, and pulse oximeter.
**Future Directions**

Randomized control trials of sevoflurane administration and FGF less than 1 L/min and 2 L/min should be performed to determine whether current FDA recommendations are valid. Changes to the restrictions of sevoflurane administration and a generic version of desflurane may further decrease the cost of both VAA. Currently, there are no reports of sevoflurane related nephrotoxicity related to low flow anesthesia in humans. New anesthesia machines are able to digitally record the amount of VAA used. With this knowledge, institutions may be able to understand provider practice and further institute and educate providers about cost savings with low flow anesthesia.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Level of Evidence</th>
<th>VAA</th>
<th>Cost/mL</th>
<th>FGF (L/m)</th>
<th>Cost</th>
<th>Method</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jellish</td>
<td>2005</td>
<td>II</td>
<td>Desflurane Sevoflurane</td>
<td>$0.75</td>
<td>2-3</td>
<td>$20.00/case</td>
<td>Dion</td>
<td>US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$0.38</td>
<td>2-3</td>
<td>$15.40/case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puckett</td>
<td>1997</td>
<td>VII</td>
<td>Desflurane Sevoflurane</td>
<td>$0.22</td>
<td>2</td>
<td>$7.85/hr</td>
<td>Vaporizer Dial Setting</td>
<td>US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$0.54</td>
<td>2</td>
<td>$7.14/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinberg</td>
<td>2010</td>
<td>VII</td>
<td>Desflurane Sevoflurane</td>
<td>$0.75</td>
<td>0.5</td>
<td>$6.42/hr</td>
<td>Dion</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1.06</td>
<td>1</td>
<td>$12.84/hr</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>$25.68/hr</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>$3.47/hr</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
<td>$6.94/hr</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>$13.88/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubarsky</td>
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<td>VII</td>
<td>Desflurane Sevoflurane</td>
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<td>Unknown</td>
<td>$18/hr</td>
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<td>US</td>
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<td></td>
<td></td>
<td>$0.68</td>
<td></td>
<td>$9/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traynor</td>
<td>2009</td>
<td>VII</td>
<td>Desflurane Sevoflurane</td>
<td>Unknown</td>
<td>N/A</td>
<td>unknown</td>
<td>MAC</td>
<td>US</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Level of Evidence</td>
<td>VAA</td>
<td>Cost/mL</td>
<td>FGF (L/m)</td>
<td>Cost</td>
<td>Method</td>
<td>Region</td>
</tr>
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<td>-----------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>Chernin&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2004</td>
<td>VII</td>
<td>Desflurane</td>
<td>$0.41</td>
<td>1</td>
<td>$6.99/hr</td>
<td>Dion</td>
<td>US</td>
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<td></td>
<td>Sevoflurane</td>
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<td>13.96/hr</td>
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<td></td>
<td></td>
<td></td>
<td>3</td>
<td>$20.97/hr</td>
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<td></td>
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<td>1</td>
<td>$5.48/hr</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
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<td></td>
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<td>2</td>
<td>$10.95/hr</td>
<td></td>
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<td>3</td>
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<tr>
<td>Golembiewski&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2010</td>
<td>VII</td>
<td>Desflurane</td>
<td>$0.96</td>
<td>1</td>
<td>$12.96</td>
<td>Dion</td>
<td>US</td>
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<td></td>
<td></td>
<td>1</td>
<td>$6.05</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2</td>
<td>$12.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3</td>
<td>$18.10</td>
<td></td>
<td></td>
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</table>
Table 2. Studies Favoring Desflurane

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Level of Evidence</th>
<th>Anesthetic</th>
<th>Flow Rate (lpm)</th>
<th>Cost/mL</th>
<th>Cost</th>
<th>Method</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobos(^7)</td>
<td>2007</td>
<td>VI</td>
<td>Desflurane</td>
<td>2.1</td>
<td>unknown</td>
<td>$33.60/hr</td>
<td>Computer Data Log</td>
<td>US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>3.4</td>
<td></td>
<td>$47.40/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockwood(^12)</td>
<td>2001</td>
<td>VI</td>
<td>Desflurane</td>
<td>1</td>
<td>unknown</td>
<td>unknown</td>
<td>Four Compartment Model</td>
<td>UK</td>
</tr>
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<td></td>
<td></td>
<td>Sevoflurane</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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</table>
Table 3. Study Claiming No Cost Difference

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Level of Evidence</th>
<th>VAA</th>
<th>FGF (lpm)</th>
<th>Cost/mL</th>
<th>Cost per case</th>
<th>Method</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boldt6</td>
<td>1998</td>
<td>II</td>
<td>Desflurane</td>
<td>1.5-2</td>
<td>$0.27</td>
<td>$7.70</td>
<td>Precision Weighing System</td>
<td>Germany</td>
</tr>
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</table>
**Table 4. Comparison of Low Flow Rates < 2 MAC hours**

<table>
<thead>
<tr>
<th>Author</th>
<th>VAA</th>
<th>FGF (L/m)</th>
<th>Cost per MAC hr</th>
<th>Method</th>
<th>Cost Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberg(^{17})</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$6.42/hr</td>
<td>Dion</td>
<td>Desflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>1</td>
<td>$6.94/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chernin(^{19})</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$3.50/hr</td>
<td>Dion</td>
<td>Desflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>1</td>
<td>$5.48/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golembiewski(^{18})</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$6.48</td>
<td>Dion</td>
<td>Sevoflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>1</td>
<td>$6.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Comparison of Low Flow Rates > 2 MAC hours

<table>
<thead>
<tr>
<th>Author</th>
<th>VAA</th>
<th>FGF (L/m)</th>
<th>Cost per MAC hr</th>
<th>Method</th>
<th>Cost Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberg</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$6.42/hr</td>
<td>Dion</td>
<td>Desflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>2</td>
<td>$13.88/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chernin</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$3.50/hr</td>
<td>Dion</td>
<td>Desflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>2</td>
<td>$10.95/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golembiewski</td>
<td>Desflurane</td>
<td>0.5</td>
<td>$6.48/hr</td>
<td>Dion</td>
<td>Desflurane</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>2</td>
<td>$12.10/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Properties</td>
<td>Sevoflurane</td>
<td>Desflurane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lowest Allowable FGF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 MAC hours</td>
<td>1 L/m</td>
<td>0.5 L/m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 MAC hours</td>
<td>2 L/m</td>
<td>0.5 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>One MAC</strong></td>
<td>2%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>200 grams</td>
<td>168 grams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>1.52 grams/mL</td>
<td>1.45 grams/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vapor Produced per mL</strong></td>
<td>183 mL</td>
<td>208 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generic</strong></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. The AHRQ Knowledge Transfer Framework

<table>
<thead>
<tr>
<th>Process</th>
<th>Knowledge creation and distillation</th>
<th>Diffusion and dissemination</th>
<th>Adoption, implementation, and institutionalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Creation of new knowledge, practices, or products</td>
<td>2a Creation of dissemination partnerships/knowledge transfer teams</td>
<td>3a Development of interventions</td>
</tr>
<tr>
<td>1b</td>
<td>Distillation of key knowledge, practices or products</td>
<td>2b Mass diffusion of key knowledge and products</td>
<td>3b Adoption and implementation</td>
</tr>
<tr>
<td>2b</td>
<td>Targeted dissemination/persuasion</td>
<td>3c Adoption and implementation</td>
<td>3d External institutionalization/routinization</td>
</tr>
</tbody>
</table>

**Knowledge and dissemination resources**
- Patient Safety Grants
  - IOM National Quality Forum
  - Expert panels
  - Professional and policy associations
- AHRQ CQIT
- AHRQ User Liaison Program
- Knowledge broker organizations (e.g., ANA, ISMP, Dart)
- Education and institutional leaders
- Professional leaders
- Dissemination partnerships
- Connector organizations

**Actors**
- Media
  - Academic journals
  - Conferences
  - Professional organizations
- Websites
- Knowledge broker organizations
  - American Nurses Association
  - Joint Commission on Accreditation of Healthcare Organizations
  - California Healthcare Foundation
  - Permanente Medical Groups
  - Pacific Health Research and Education Fund
  - Kaiser Permanente
  - Health improvement organizations
  - Healthcare organizations
  - Patient advocates
  - Public policy advocates

**Target Audiences**
- Adoption and implementation
  - Healthcare organizations
  - Patients
  - Patient advocates
  - Public policy advocates

**Activities**
- Evidence summaries/syntheses papers
- Research projects
- Consensus processes for priorities
- Academic publications
- Conference presentations
- Fact sheets
- Press releases
- Websites
- General communication materials
- Workshops/Webcasts
- Audience analysis
- Segmentation analysis
- Funder analysis
- Stakeholder analysis
- Partnership and GTT development
- Tailored messages and communications
- Intervention packages
- Implementation tools
- Training
- Cultural assessments
- Technical assistance
- Help line user groups
- Organizational communications
- Internal stakeholder analysis
- Cost-benefit analysis
- Standards and guidelines
- Monitoring and measurement tools
- Institutional policy changes
Appendix 1: IRB Approval

TCU INSTITUTIONAL REVIEW BOARD
Approval Form

Institutional Review Board (IRB) approval refers to research involving human subjects whether on or off campus. Significant changes in design, participants, or measures must be approved by the IRB. Multi-year projects must be submitted annually for approval. Any unexpected adverse effects on human subjects due to the procedure should be reported immediately.

Date: 09/17/2012

Principal Investigator: John Varnavski

Project Title: Cost Analysis of Desflurane and Sevoflurane

Multi-Year Project: Yes [ ] No [x]

Approval Number: DRB-F12-11

Proposed Participants:
- [ ] TCU students, faculty, or staff
- [x] Non-TCU Participants
- [ ] Special populations (e.g., children) — specify ____________________________

Comments:

Approvals Period: 09/17/2012 - 11/1/2012

Committee Decisions:
- [ ] Approved, Minimal Risk
- [ ] Approved, Expedited
- [x] Conditional Approval, with following stipulations:

- [ ] Not Approved, Comments:

Chair ____________________ Date ____________________
Appendix 2: Level of Evidence Table

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs), or evidence-based clinical practice guidelines based on systematic reviews of RCTs</td>
</tr>
<tr>
<td>Level II</td>
<td>Evidence obtained from at least one well-designed RCT</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence obtained from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>Level IV</td>
<td>Evidence from well-designed case-control and cohort studies</td>
</tr>
<tr>
<td>Level V</td>
<td>Evidence from systematic reviews of descriptive and qualitative studies</td>
</tr>
<tr>
<td>Level VI</td>
<td>Evidence from single descriptive or qualitative study</td>
</tr>
<tr>
<td>Level VII</td>
<td>Evidence from the opinion of authorities and/or reports of expert committees</td>
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</tbody>
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References


