NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **EAC assessment report addendum** – an addendum to the EAC assessment report produced by an external assessment centre who have reviewed and critiqued the available evidence.
3. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
6. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
7. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
8. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

9. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

External Assessment Centre report

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Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Glossary

Term	Definition
Anxiolysis	Relieving anxiety.
Dead Space	In the context of ventilation equipment, the volume of equipment that contributes to the rebreathing of air (i.e. that is located between the patient and the expiratory limb of the ventilator).
Iatrogenic	Negative effects, such as illness, caused by medical examination or treatment.
Inhaled Sedation	See 'Volatile Sedation' below.
Minimum Alveolar Concentration	Is a unit measures of volatile sedatives, defined as the end-expiratory concentration needed to prevent a motor response in 50% of patients to a standard surgical stimulus.
Pa_{O2}/FIO2 ratio	A measure of how well the patient's arterial blood is oxygenated compared to the concentration of oxygen a patient is receiving.
Tidal Volume	The volume of air moved between an inhalation and an exhalation.
Volatile Sedation	Sedation via inhaled compounds, often described as inhaled sedation.

Abbreviations

Term	**Definition**
ANOVA	Analysis of Variance
ARDS	Acute Respiratory Distress Syndrome
BIS	Bispectral Index
BMI	Body Mass Index
BNF	British National Formulary
CABG	Cardiac Artery Bypass Graft
CAM-ICU	Confusion Assessment Method for The Intensive Care Unit
CI	Confidence Interval
CK	Creatinine Kinase
CKMB	Creatinine Kinase Myocardial Band
COPD	Chronic Obstructive Pulmonary Disease
CO_2	Carbon Dioxide
CPB	Cardiopulmonary Bypass
CPR	Cardiopulmonary Resuscitation
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
ECMO	Extracorporeal Membrane Oxygenation
FETt%	Fractional End-Tidal Concentration
GCS	Glasgow Coma Scale
HME	Heat and Moisture Exchanger
ICU	Intensive Care Unit
IQR	Interquartile Range
IV	Intravenous
LOS	Length Of Stay

Term	Definition
MAC	Minimum Alveolar Concentration
MAP	Mean Arterial Pressure
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE Clinical Guideline
NICE MTG	NICE Medical Technology Guidance
NICE QS	NICE Quality Standard
O_2	Oxygen
PaO_2	Partial Arterial Pressure of Oxygen
pCO_2	Partial Pressure of Carbon Dioxide
PPM	Parts Per Million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
PTSD	Post-Traumatic Stress disorder
QUORUM	Quality of Reporting of Meta-Analyses
RASS	Richmond Agitation-Sedation Scale
RCT	Randomised Controlled Trial
ROSC	Return Of Spontaneous Circulation
SCCU	Surgical Coronary Care Unit
SD	Standard Deviation
TTM	Targeted Temperature Management
TV	Tidal Volume
VAS	Visual Analogue Scale
vs	Versus

Executive summary

AnaConDa-S (and the predecessor model, AnaConDa) is a device attached to the breathing circuit connecting a patient to a mechanical ventilator, allowing for the delivery of volatile sedation with isoflurane or sevoflurane. This assessment report compares the use of AnaConDa-S delivered sedation to other methods of delivery of volatile sedation to patients managed on the intensive care unit (ICU) and to standard of care intravascular (IV) sedation. The EAC identified 12 randomised control trials and 9 non-randomised, comparative studies comparing AnaConDa delivered sedation to IV sedation (standard of care). No evidence comparing AnaConDa to other methods of delivery of volatile sedation on ICUs was identified. This allows the EAC to comment on the potential benefits of AnaConDa-S delivered sedation to IV sedation only. Clinical evidence indicates that AnaConDa delivered volatile sedation is associated with faster wake-up and extubation times although it should be noted that the clinical benefits cannot be attributed specifically to the action of the device itself.

Inhaled sedation with isoflurane or sevoflurane, delivered using the AnaConDa-S device is cost saving compared with IV sedation with propofol. The cost savings with sevoflurane were less than with isoflurane, however clinical expert input suggests that isoflurane is more relevant to NHS practice. The key driver for the cost savings is the duration of ICU stay, including the duration of mechanical ventilation. While there is some uncertainty about the robustness of key inputs including ICU stay duration and duration of mechanical ventilation, EAC sensitivity analysis indicated that as long as AnaConDa-S inhaled sedation (isoflurane) results in a 0.2-day shorter ICU stay compared with propofol, it will be cost saving.

Compared with IV sedation, volatile sedation delivered using the AnaConDa device results in faster wake-up and extubation times and using the AnaConDa device to deliver inhaled sedation is cost-saving if duration of ICU stay is shorter.

The EAC conclusion is that the AnaConDa device offers clinicians a tool for the delivery of an alternative sedation strategy to help them manage complex patients receiving critical care.

1 Decision problem

The company submission agreed with the scope issued by NICE on the target population. The company also commented on the other aspects of the decision problem, which are outlined in Table 1. Briefly, the company proposed to treat AnaConDa-S and AnaConDa as the same intervention, highlighted which evidence is limited and that staff time would only be considered in the economic analysis while amount of sedative used and staff exposure would only be considered in the environmental impact assessment. They noted that in the economic analysis they would only consider a comparison with standard intravenous (IV) sedation. The EAC noted that even though the company did not have any comments on the relevant subgroups, their search strategy excluded evidence from those under the age of 18 years. The company stated that current regulation does not cover paediatric sedation with volatile agents in the intensive care setting, yet clinical experts noted that the regulation does not cover the use of volatile sedatives for adult patients in this setting either (see correspondence log). These volatile agents are though indicated for the induction and maintenance of anaesthesia and are already used off-label in the intensive care setting (see correspondence log). Sedana Medical has made submissions to the MHRA and the European Medicines Agency for approval of isoflurane sedation via AnaConDa for adult patients.

Table 1: Summary of company comments on the decision problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	People who are invasively ventilated in intensive care using a mechanical ventilator but not a high frequency ventilator.	None.	The EAC notes that the company restricted its search strategy to only the adult population. The EAC has included the paediatric population in its search strategy.
Intervention	AnaConDa-S AnaConDa (previous version)	Company notes that these are the same intervention. They reference Marcos-Vidal et al. (2020) and Bomberg et al. (2018) stating that sedation efficiency is comparable between the two devices, but that the use of AnaConDa-S results in lower carbon dioxide rebreathing.	The EAC accepts the company's claim that the two device versions can be treated as the same intervention. See section 2 (Overview of Technology) for further detail regarding the differences between both device versions.

Comparator(s)	IV sedatives Standard vaporiser	The company notes that direct evidence is available for inhaled sedation via AnaConDa compared to IV sedatives, but that the AnaConDa device is not compared with other means of delivering inhaled sedation.	The EAC notes that in their submission, the company has included evidence from other technologies that deliver volatile sedatives.
Outcomes	a. wake-up time after sedation b. cognitive recovery c. sedation efficacy (time to extubating, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale) d. markers of cardiac injury, liver, gut, kidneys and brain for short-term operative sedation e. sedation effectiveness in patients with life-threatening bronchospasm and asthma f. oxygenation and inflammatory markers in patients with ARDS g. psychological outcomes (e.g. memories of hallucination, and long-term psychological morbidity, PTSD) h. effectiveness of ventilation on people with bronchoconstriction i. reduction of additional bronchodilators j. duration of mechanical ventilation/ increased ventilator-free days k. length of stay in the intensive care unit (ICU) l. hospital length of stay/ hospital-free days. m. amount of volatile anaesthetic agent used n. staff exposure to volatile anaesthetic agents o. staff time in the ICU p. amount of opioid drug used q. device-related adverse events	The company noted that: Much evidence is available for a, b, c, j, k, p and q. Evidence is limited for d, e, f, g, h, I and l. They only considered o in the economic submission. Points m and n are only considered in the environmental impact and sustainability considerations.	The EAC note that the outcomes considered in the economic model include duration of mechanical ventilation and duration of ICU stay as well as staff time in the ICU as stated by the company.
Cost analysis	Costs will be considered from an NHS and personal social services perspective.	The company notes that inhaled sedation via AnaConDa device will be compared with standard-of-	Costs in the model compare inhaled sedation (isoflurane) with IV sedation (propofol) as

	The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	care IV sedation only. Additionally, while different cost scenarios of uptake of the AnaConDa device will be included, analysis of different combinations of devices will not be included.	the base-case. Clinical expert input suggest this choice of drugs is likely most reflective of UK practice. The economic model compares costs of inhaled sedation delivered using the AnaConDa device only with IV sedation (standard of care). No other devices have been included and the EAC consider this to be appropriate as there is no evidence comparing inhaled sedation using AnaConDa to other devices.
Subgroups	People with acute asthma that need to be mechanically ventilated. People with acute respiratory distress syndrome that need to be mechanically ventilated Children that need to be mechanically ventilated Patients who need to have regular neurological wake up tests performed People who are intolerant to IV sedation (e.g. people who misuse alcohol, people who misuse drugs, people on overdose, people with COVID-19) People with hepatic and renal failure People with super-refractory status epilepticus People under prolonged sedation who need an IV sedation break (due to being at risk of developing tolerance, tachyphylaxis and/or propofol infusion syndrome)	None	The EAC notes that despite children being highlighted as a relevant subgroup the company's search strategy excluded evidence pertaining to this subgroup. The EAC has included evidence concerning children in its own search strategy.

2 Overview of the technology

The Anaesthetic Conserving Device-S (AnaConDa-S; Sedana Medical) is a volatile sedative delivery system to give isoflurane or sevoflurane to people who are invasively ventilated, usually in an intensive care setting. AnaConDa-S can be used with almost any kind of ventilator, except high-frequency ventilators. The AnaConDa device was originally launched in the UK in 2005 but was replaced in 2017 with the AnaConDa-S. The original is still available on request. The AnaConDa-S has a lower dead space of 50ml compared with 100ml in the original device. It can work with tidal volumes as low as 90ml and the lower dead space allows it to be used on smaller adults or children who have smaller minute or tidal ventilation. Otherwise the company has confirmed the mechanism of action is the same in both devices. As such, the two device models are assumed to be equivalent to each other for the purposes of this report (see section 5.3 for details).

AnaConDa-S is a single-use device which can be inserted into either the breathing circuit of a ventilator between the endotracheal tube and Y-piece (standard placement), replacing the heat and moisture exchanger (HME) or in the inspiratory port of the ventilator (alternative placement). Liquid sedative (isoflurane or sevoflurane), is injected through the sedative agent line, into a porous rod in the AnaConDa-S device where the sedative is vaporised. The vaporised sedative is then inhaled by the patient. With continued breathing, the majority of sedative agent that has not been absorbed by the lungs is exhaled and absorbed by an active carbon filter in the device. On further inhalation, the sedative is desorbed from the filter and transported back to the lungs, reducing the amount of sedative agent wasted. The AnaConDa-S device also contains a bacterial and viral filter and a gas analyser port. This port is used to measure the exhalated sedative concentration in minimal alveolar concentration (MAC value) or end-tidal concentration (FET%). Gas monitors, which can measure concentrations of carbon dioxide and sedative gases, must be used to continually monitor sedation, and will need to be purchased separately if not already available. AnaConDa-S is also

recommended to be used with a gas scavenging system connected to both the ventilator and the multi-gas analyser unit. This can be either via a passive system like the manufacturer's FlurAbsorb and FlurAbsorb-S products, or via an active scavenging system.

The AnaConDa-S device needs to be changed every 24 hours or more frequently if required. Additionally, if the FlurAbsorb or FlurAbsorb-S system is used for scavenging, then this needs to be replaced as well. FlurAbsorb-S needs to be replaced after 24h or when 3 syringes (150ml) have been used, while FlurAbsorb has a capacity of 10 syringes (500ml) and does not require changing every 24h; only one scavenging product can be used at a time. The scavenging system used might require more frequent changes if the AnaConDa-S is used in the alternative placement together with a wet circuit.

It should be noted that when positioned in the alternative placement, the device cannot function as an HME or reflect the sedative agent back to the patient resulting in the need for higher rates of sedative and higher concentrations being expelled from the ventilator. Furthermore, the sampling port cannot be used for monitoring drug concentration levels. Other means of humidifying the circuit or monitoring drug concentration levels need to be employed in this situation. The company, however, has suggested that AnaConDa-S is very rarely used in the alternative placement (see correspondence log). They also noted that since it is used in this placement to minimize dead space, it is usually used for patients with low tidal volumes (such as smaller patients or those undergoing extracorporeal membrane oxygenation) who require lower infusion rates of the sedative; this means that in practice similar sedative infusion rates are likely to be used when the device is placed in both positions. As such, the amount of the sedative agent expelled from the ventilator would not be notably larger than when used in the standard position, and the use of a scavenging system will protect staff from exposure to the sedative agent.

The intended place in therapy for AnaConDa-S would be as an alternative to IV sedation. It is expected to provide more flexible clinical management due to

faster patient wake-up and cognitive recovery, which enables reduced time to extubation, less time on a ventilator and faster discharge from ICU/hospital.

The manufacturer has provided CE marking documentation for the device and associated accessories (not specified), both of which are classed as Class IIa medical devices. The current certification (CE 667826) was first issued on 09/02/2017, though it is noted that a previous certification also existed for the device (CE 94203). The expiry date for the certification is 26/05/2024, but from 2023 products used in the UK will require a UK conformity assessment (UKCA). The manufacturer stated that they will have a designated Responsible Person in the UK from September 2021 to comply with the new rules and will apply for the UKCA nearer the 2023 deadline.

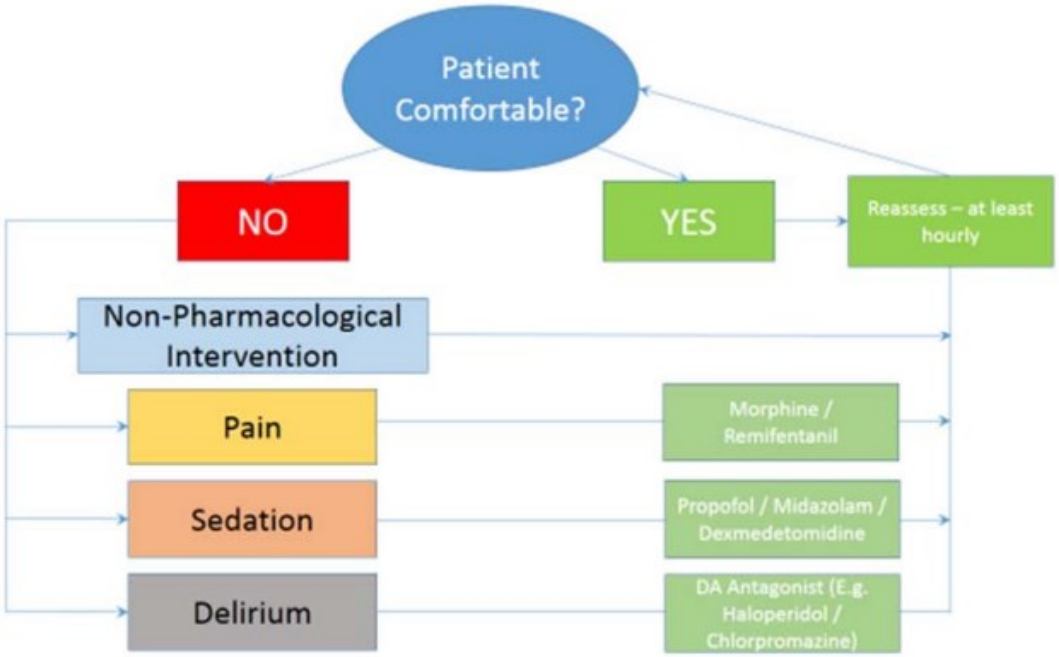
3 Clinical context

Sedatives are frequently (>85% of patients) administered to critically ill patients to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm (Weinert et al., 2007; Jerath et al., 2017; Devlin et al., 2018). Sedation therefore can imply anything from anxiolysis to the induction of a state of unresponsiveness (Grounds, 2014). Sedation is not a substitute for analgesia and should not be prolonged beyond clinical need to avoid iatrogenic harm.

Sedation in mechanically ventilated ICU patients is generally achieved by the IV infusion of propofol, midazolam or dexmedetomidine, in combination with opioids (Grounds, 2014; Devlin, 2018). Sedation is used to achieve a defined Richmond Agitation & Sedation Scale (RASS) score (with lower values implying deeper sedation) for each patient. In general, lighter sedation is preferred if possible (Devlin, 2018; Arora 2018), but this is not appropriate for all patients and can be difficult to achieve (see correspondence log). Optimal sedation creates tolerance for the endotracheal tube, allows for spontaneous breathing and minimizes iatrogenic harm. Patients for whom deeper sedation might be required include respiratory failure patients requiring pharmacological paralysis to facilitate optimal mechanical ventilation (see correspondence log). Light sedation is variously defined, but most texts agree

that a score below -2 implies deep sedation (Grounds, 2014; Devlin, 2018). The general framework for providing analgesia in the UK ICU setting is presented Figure 1 below and is taken from a 2014 guideline of the Intensive Care Society.

Figure 1: General analgo-sedation framework (with a non-exclusive list of drugs) from Grounds, 2014.



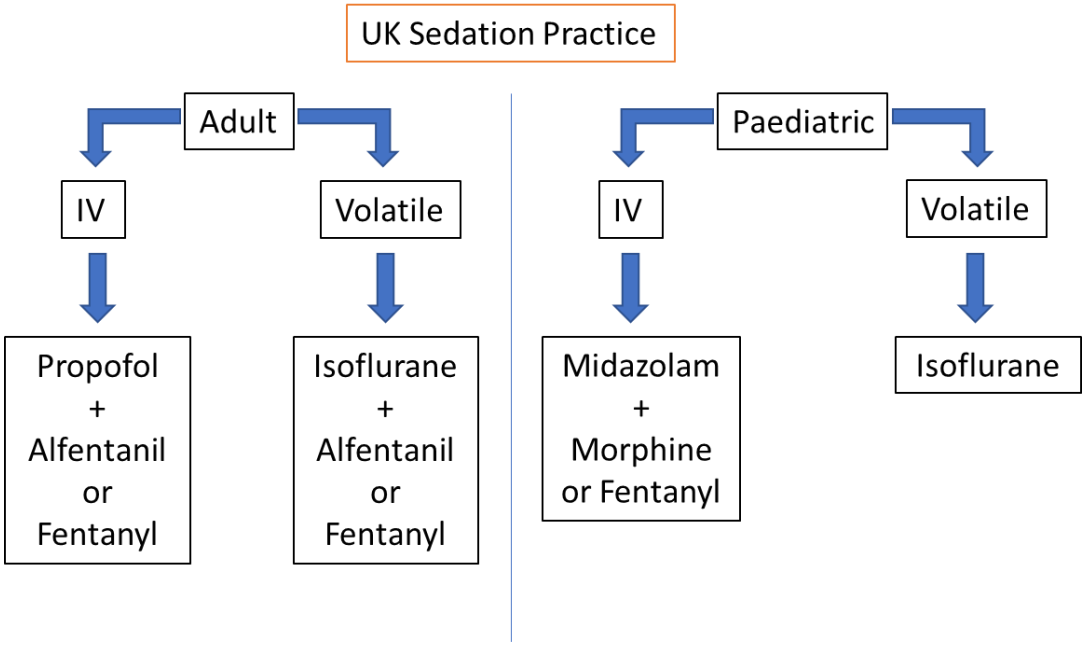
The UK's Intensive Care Society has in 2014 published guidance on the use of analgesia and sedation in critical care (Grounds, 2014). This guidance highlights that propofol has gained popularity as a sedative agent, and clinical experts have confirmed that it is the sedative of choice in UK adult ICUs (see correspondence log). The experts further highlighted that the use of propofol as a sedative is also recommended in the USA Society of Critical Care Medicine guideline on Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (Devlin 2018). Importantly, propofol is used alongside an opiate analgesic, usually alfentanil or fentanyl (see correspondence log). A paediatric intensivist noted (see correspondence log) that in paediatric ICU patients midazolam is the main sedative that is used together with morphine

or alfentanil. The paediatric expert also noted that in children the comfort score is used for assessing sedation depth rather than RASS.

Grounds (2014) highlights that AnaConDa together with scavenging systems can make the administration of volatile anaesthetics safer for ICU staff. Grounds (2014) also states that isoflurane is a potent bronchodilator of value in treating those with bronchospasms, referencing Johnston (1990). The joint 2019 Scottish Intercollegiate Guidelines Network and British Thoracic Society British guideline on the management of asthma (SIGN158) highlights that there is some limited evidence supporting the use of sevoflurane in the management of children with life-threatening asthma (referencing Schutte 2013), while stating intubation and invasive ventilation is standard practice in life-threatening asthma episodes. Grounds (2014), nevertheless, notes that fluoride accumulation and dependency with ventilation are potential problems with the use of volatile agents. The clinical experts (see correspondence log) did not believe any of these issues to be of major importance, agreeing unequivocally that the only absolute counterindication for the use of volatile sedation in the ICU would be a history of malignant hyperthermia.

Clinical experts (see correspondence log) have noted that, with the exception of one expert who uses sevoflurane, they all use isoflurane for sedation with AnaConDa-S. They also stated that in adult patients the volatile sedative would be used alongside the opiate, while in paediatric patients the volatile sedative would usually be used without an additional opiate. Figure 2 summarises sedation practice in the UK based on the available guidance and expert opinion. It is important to highlight that this represents the usual practice, as understood by the EAC based on the available guidance and expert opinion, and not a strict clinical pathway. The ICU patient population is highly heterogeneous with respect to both demographics and clinical need, often with complex medical needs involving several organ systems. As such, ICU clinicians often need to adjust their practice to match the requirements of these complex patients, making it impossible to prescribe strict pathways that would accommodate for this diverse patient population.

Figure 2: Diagram representing standard UK sedation practice.



The company states that AnaConDa-S would be most beneficial in patients requiring deeper sedation for over 12 hours, but does not restrict its use to this patient group. They noted that volatile sedation delivery via the AnaConDa-S system would benefit patients with abnormal hepatic and renal function; those who would benefit from liver or kidney independent sedative elimination; and those with a contraindication to the use of opioids. Furthermore, the manufacturer highlights that AnaConDa-S delivered sedation might be beneficial to the following patient groups:

- those suffering from bronchospasms, due to the bronchodilatory effects of the volatile agent used
- those difficult to sedate due to alcohol or drug misuse
- patients requiring deep but rapidly reversible sedation
- those requiring sedation but also frequent neurological assessments
- those at risk of iatrogenic harm from IV sedatives

The EAC believes that the company's description of the clinical context is appropriate and relevant to the decision problem under consideration. It is

though important to remember, as the clinical experts have noted (see correspondence log), that the clinical benefit of the intervention will be due to the volatile sedative delivered via the AnaConDa-S and not due to the device itself.

Special considerations, including issues related to equality

MIB229 on AnaConDa-S notes that volatile anaesthetics might have potential teratogenic effects and can affect foetal development. As such, the use of AnaConDa-S might be contra-indicated in pregnant women. The EAC clarified this point with the clinical experts (see correspondence log), who indicated that volatile agents have been used in the past in pregnant women and that any danger to the developing foetus would be weighed against the medical risk to the woman. As such, there is no absolute counterindication of the used of AnaConDa-S in pregnant women.

MIB229 also notes that volatile anaesthesia might be of particular benefit to children and that pregnancy and age are protected characteristics under the 2010 Equalities Act.

In light of NICE guideline CG52, it was discussed with clinical experts (see correspondence log) whether AnaConDa-S could be used in those suffering from opioid addiction, in whom total withdrawal of opioids might not be desirable. CG52 covers the issue of opioid detoxification in those over 16 years old. Briefly, the guideline discourages the use of ultra-rapid, rapid and accelerated detoxification which utilise opioid antagonists, highlighting potential issues with adverse events and withdrawal symptoms. The EAC wanted to clarify whether using volatile sedation would result in problems relating to withdrawal syndromes in this patient group due to potentially different use of opioid medication with volatile sedation. The experts stated that they do not see any reason why the use of AnaConDa-S would be contraindicated in these patients. Later on, the experts also highlighted that opioids are used alongside volatile sedation in the adult population.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company conducted a broad search encompassing efficacy, safety, and tolerability evidence for inhalational versus intravenous sedatives among mechanically ventilated adult patients in ICU. The search was not restricted by sedative drug or by type of device used to support inhalational sedatives.

The search was conducted across three databases, identifying a total of 3406 references after deduplication. Although the search strategies were comprehensive using a combination of free text terms and indexed terms, it was not focused on the key concepts of the scope as indicated in the company's inclusion and exclusion criteria. This was further evidenced in the search strategies which failed to include the term 'anaconda' but did include specific terms for different types of sedatives. As the key scope concepts had not been adequately captured and combined in the search strategies, the EAC were not confident that all relevant literature had been identified and therefore conducted their own systematic searches. Details of the company and EAC searches are provided in appendix A. The EAC literature searches identified 463 references, these were independently screened by title and abstract in accordance with the scope by two researchers. Of these, 50 were selected for further screening and full texts were retrieved and reviewed again by two researchers, and disagreements on inclusion were discussed until a consensus was reached. All studies included by the company were also checked for eligibility against the scope before final selection for inclusion was concluded. Study selection flow diagrams, outlining the number of studies excluded at each stage for both the company and EAC, are available in appendix A.

The inclusions and exclusion criteria applied by the company are summarised in table 2. Broadly, the company included all randomised controlled trials (RCTs) that compared volatile sedation to IV sedation in the adult population. The EAC noted that the NICE scope also included the use of the device in the paediatric population and that only studies where the intervention has been

delivered via AnaConDa-S are of relevance to the decision problem. The EAC also considered cohort studies and comparative case series as providing relevant information and restricted inclusion to only those studies available in English.

Table 2 Company study selection criteria

Inclusion Criteria		
Participants	Mechanically ventilated adult patients (>18 years) requiring sedation	
Interventions	• Isoflurane • Sevoflurane • Desflurane	
Comparators	• Placebo • Any included intervention • Propofol • Dexmedetomidine • Clonidine	• Midazolam • Lorazepam • Haloperidol • Morphine
Study Design	RCTs irrespective of blinding status	
Language	No restriction on language	
Publication timeframe	Database inception to present	
Exclusion Criteria		
Participants	• Animal/In-vitro • Disease not of interest (not specified)	
Interventions	None listed	
Comparators	None listed	
Study Design	None listed	
Language	None listed	
Publication timeframe	None listed	

4.2 *Included and excluded studies*

The company submission included 25 studies from 26 publications (Rohm 2008 and Rohm 2009 reported on the same study), including one unpublished study. The EAC largely agreed with the inclusions in the company

submission, including a total of 16 studies (17 publications) from the ones included by the company. The EAC excluded 9 of the studies included by the company, eight because the volatile sedation was not delivered through AnaConDa-S (Bellgardt 2019, Daume 2021, Gomez 1995, Guinot 2020, Kong 1989, Meiser 2003, Millane 1992, Spencer 1992) and one because it focused on the use of bispectral index monitoring (BIS) rather than comparing the effectiveness of different sedation strategies (Sackey 2007).

The company submission also referred to four meta-analysis (Landoni 2016, Jerath 2017, Kim 2017, Spence 2017), of which only Kim (2017) included solely studies where volatile sedation was delivered via AnaConDa. Since all of the individual studies included in these meta-analysis that utilised AnaConDa are already included in the EAC's analysis (except Sackey 2008, which is a follow-up of a subset of patients from Sackey 2004; neither was it included in the company's submission), the meta-analysis results were not extracted as this would result in some study results being considered more than once by the EAC. More detail on the meta-analysis carried out by Kim (2017) is given in section 7.

The EAC identified six additional publications describing studies relevant to the scope of this assessment. The EAC included two studies referenced in NICE MIB229 that compared the classical AnaConDa with the AnaConDa-S (Bomberg 2018, Marcos-Vidal 2020). Information on the comparability of the two devices was necessary to assess the company's statement they could be regarded as the same intervention. One publication (Hellstrom 2011) reported additional outcomes of a study already included in the company's submission (Hellstrom 2012). The remaining three additional studies included by the EAC all compared AnaConDa-S delivered volatile sedation to IV sedation and reported relevant outcomes (Foudraine 2021, Jung 2020, Meiser 2018). This brought the total of reported studies to 21 (23 publications). A comparison of the studies included by both the EAC and the company is presented in table 3.

A list of conference abstracts identified as relevant by the EAC and their summaries can be found in appendix C. The EAC excluded one abstract listed by the company (El 2016) as it did not state whether the study utilised the AnaConDa.

Table 3: Company and EAC study selection comparison

Study	Included in Company Submission	Included in EAC Assessment Report	EAC Comment
Bellgardt 2016	✓	✓	No change
Bellgardt 2019	✓	X	Volatile sedation was not delivered via AnaConDa
Bomberg 2018	X	✓	Study referenced in NICE MIB229. Data extracted to assess comparability between the classical AnaConDa and AnaConDa-S, but data not used to assess the technologies effectiveness against the comparator.
Daume 2021	✓	X	Volatile sedation was not delivered via AnaConDa
Foudraine 2021	X	✓	Study compares volatile sedation delivered via AnaConDa to IV sedation and has relevant outcomes.
Gomez 1995	✓	X	Volatile sedation was not delivered via AnaConDa; study in Spanish.
Guerrero Orriach 2013	✓	✓	No change.
Guinot 2020	✓	X	Volatile sedation was not delivered via AnaConDa
Hanafy 2005	✓	✓	No change.
Hellstrom 2011	X	✓	Study has relevant outcomes additional to those of Hellstrom 2012.
Hellstrom 2012	✓	✓	No change.
Jabaudon 2017	✓	✓	No change.
Jerath 2015	✓	✓	No change.
Jerath 2017	✓	X	Meta-analysis excluded as it includes some studies using non-AnaConDa delivered volatile sedation. Relevant studies already included.
Jung 2020	X	✓	Study compares volatile sedation delivered via AnaConDa to IV sedation and has relevant outcomes.
Kim 2017	✓	✓	No change; meta-analysis.
Kong 1989	✓	X	Volatile sedation was not delivered via AnaConDa
Krannich 2017	✓	✓	No change.
Landoni 2016	✓	X	Meta-analysis excluded as it includes some studies using non-AnaConDa delivered volatile sedation. Relevant studies already included.
Marcos-Vidal 2014	✓	✓	No change.
Marcos-Vidal 2020	X	✓	Study referenced in NICE MIB229. Data extracted to assess comparability between the classical AnaConDa and AnaConDa-S, but data not used to assess the technologies effectiveness against the comparator.
Meiser 2003	✓	X	Volatile sedation was not delivered via AnaConDa
Meiser 2018	X	✓	Study compares volatile sedation delivered via AnaConDa to IV sedation and has relevant outcomes.
Mesnil 2011	✓	✓	No change.
Millane 1992	✓	X	Volatile sedation was not delivered via AnaConDa

Rohm 2008	✓	✓	No change.
Rohm 2009	✓	✓	No change.
Sackey 2004	✓	✓	No change.
Sackey 2007	✓	X	Study focuses on assessing the use of Bispectral Index monitoring and not on comparing volatile and IV sedation
SED001 unpublished	✓	✓	Unpublished trial with data supplied by the manufacturer
Soro 2012	✓	✓	No change.
Spence 2017	✓	X	Meta-analysis excluded as it includes some studies using non-AnaConDa delivered volatile sedation. Relevant studies already included.
Spencer 1992	✓	X	Volatile sedation was not delivered via AnaConDa
Staudacher 2018	✓	✓	No change.
Steurer 2012	✓	✓	No change.
Turktan 2019	✓	✓	No change.

The EAC notes that none of the included studies were carried out in the UK and that all studies were carried out in the adult population. While all studies use the AnaConDa-S as the intervention, some studies use isoflurane and some sevoflurane as the sedative agent. Similarly, various different IV agents are used in the studies. In the UK, there is no strict pathway for patient sedation but expert opinion (see correspondence log) indicates that isoflurane is the most commonly used agent with AnaConDa-S while propofol is the IV agent of choice in the adult population. Moreover, the way that sedation depth has been assessed varies throughout these studies. As such, while all the included studies match the scope of this assessment, they will all be of different relevance to the decision problem.

A high-level summary of the included studies (full publications and the unpublished SED001 trial) is presented in table 4. It should be noted that the traffic light system used in table 4 relates only to whether the study can be considered applicable to the decision problem as outlined in the scope and, while briefly highlighting some of the potential limitations and areas for concern, is not a quality appraisal. Critical appraisal of all included studies is reported in section 5.2 and appendix B.

Table 4: Comparative Studies

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
AnaConDa versus AnaConDa-S				
Marcos-Vidal (2020) **Location**: Spain **Setting**: ICU	Comparative crossover study of the AnaConDa and AnaConDa-S devices. • Intervention: AnaConDa-S (sevoflurane) • Comparator: AnaConDa (sevoflurane) **Inclusion criteria;** • Patients >18 years of age undergoing scheduled coronary surgery with cardiopulmonary bypass (CPB) **Exclusion criteria** • Body Mass Index (BMI) >35 kg/m^2 • Hypoxemic respiratory failure after CPB • History of moderate to severe pulmonary hypertension • History of chronic obstructive pulmonary disease (COPD) • History of alcohol or psychotropic drug abuse • History of malignant hyperthermia **Procedure**: Both devices were used sequentially for 60 minutes to assess efficiency of sevoflurane (SEV) reflection and compare blood gas measures. Patients were ventilated	23 post cardiac surgery patients sequentially sedated with each device for 60 minutes each **Patient demographics:** • Male – n=20 (87%) • Mean weight - 75.42kg • Mean height – 164.48cm • Mean BMI – 27.85 kg/m^2 • Mean idealised weight – 60.61kg ● (Green)	• Arterial blood gasses • Bispectral Index (BIS) ● (Green)	Sample size/statistical power estimation performed at outset Did not compare to standard care (IV sedation) Not UK/NHS setting Short term sedation only No funding information was provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	with tidal volumes (TV) of 5ml/kg of ideal body weight for first 30 mins and then 7ml/kg for the next 30 mins. **Statistical analysis:** For paired data, students t-test and an analysis of variance (ANOVA) with Bonferonni post-hoc correction was performed. For qualitative variables chi-square test was used. **Status**: Published **Funding**: Not reported **Conflicts of interest**: Disclosed – none reported ● (Amber)			
Bomberg (2018) **Location**: Germany and USA **Setting**: critical care	Comparative crossover study evaluating whether AnaConDa-S reduced carbon dioxide CO_2 retention and ventilatory demanded during sedation compared to AnaConDa ● Intervention: AnaConDa-S (sevoflurane) ● Comparator: AnaConDa (sevoflurane) **Inclusion criteria:** ● Critically ill patients requiring deep sedation	10 critically ill patients requiring deep sedation were evaluated. **Patient demographics:** ● Male – n=3 (30%) ● Mean age – 59 years ● Mean height – 167cm ● Mean body mass index – 29 kg/m^2 ● (Green)	Outcomes documented every 15 minutes. Results reported at successive timepoints (24h, 1h, 2h, 1h, 2h): ● Isoflurane consumption ● Blood gas analysis ● Cardiac markers	Small sample size Did not compare with standard care (IV sedation) Not UK/NHS setting

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Exclusion criteria: Not reported **Procedure**: AnaConDa was primed with 1.2ml isoflurane and adjusted to reach a Richmond Agitation Sedation Scale (RASS) score between -3 and -4. After 24hr sedation a 5hr observation period started. After 1hr AnaConDa-S was used, primed with 0.9ml isoflurane, and measurements continued for 2 hrs. A new primed AnaConDa was then connected for a further 2hrs. **Statistical analysis:** Analysis of change in continuous variables was assessed using an ANOVA for repeated measurements with Bonferroni corrections for multiple testing. Friedman test was used for data not normally distributed followed by Bonferroni corrections. **Status**: Published **Funding**: AnaConDa-S reflectors provided by Sedana Medical **Conflicts of interest**: Two authors received honoraria and travel expenses from Sedana. One of these authors has also been a consultant for Sedana and received		● (Green)	

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	honoraria, travel expenses and research funding from Pall Medical. ● (Amber)			
Volatile sedation with AnaConDa versus standard of care (IV sedation)				
Sackey 2004 **Location:** Sweden **Setting**: Multidisciplinary university Intensive Care Unit (ICU) **Date**: January 2002- July 2003	Randomised Controlled Trial (RCT) to test the efficacy and patient safety of administration of isoflurane for prolonged sedation in an ICU compared to intravenous (IV) midazolam **Intervention**: AnaConDa (isoflurane) **Comparator**: IV midazolam **Inclusion criteria:** ● 18-80 years old ● Ventilator dependent ● Expected to require >12 hours sedation **Exclusion criteria:** ● Evidence of intracranial pathology ● Family history of malignant hyperthermia ● Need dialysis at inclusion ● Pregnancy ● Continuous sedation had been administered for >18 hours before inclusion	40 ventilator dependent ICU patients aged 18-80 years expected to need >12 hours sedation Intervention: n=20 Comparator: n=20 **Patient demographics:** Intervention ● Median age - 60 years ● Male - n=9 (45%) Comparator: ● Median age – 60 years ● Male – n= 12 (60%) ● (Green)	● Sedation efficacy ● Sedative infusion rates ● Time to extubate ● Cognitive recovery ● ICU length of stay ● Adverse events ● (Green)	Not UK setting Midazolam is not the sedative of choice in the UK for the adult population. No conflict of interest information was provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Procedure: Patients were randomised to receive either isoflurane via AnaConDa or IV midazolam. After randomisation, all other sedatives were terminated. Isoflurane was infused to the AnaConDa at a concentration of 1.0-3.5mL/hr and midazolam in the dose range of 0.02-0.05mg/kg/hr. Infusion rates were adjusted thereafter on a patient by patient basis to achieve the desired sedation level (Bloomsbury Sedation Scale of -1 to +1). Study duration was 96 hours. At this point, patients were extubated if medically ready. For patients not ready for extubation at 96 hours, the study sedation was terminated and standard practice at that unit would continue. **Statistical analysis:** Differences between groups were analysed using a student's t-test or a Wilcoxon test. For wake-up time, a multiple regression analysis was performed adjusting for the following variables; duration of sedation, age, acute physiology and chronic health score, opioid requirement, % time with over sedation and sedation before randomisation. **Status:** Published **Funding:** Supported in part by Hudson RCI who provided the AnaConDa devices and by Abbott Scandinavia who supplies the isoflurane.			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Conflicts of Interest: Not reported ● (Green)			
Hanafy (2005) **Location**: Egypt **Setting**: Surgical Coronary Care Unit **Date**: May 2010-September 2013	RCT comparing isoflurane to midazolam postoperative sedation after coronary artery bypass grafting (CABG). **Intervention**: AnaConDa (isoflurane) **Comparator**: IV midazolam **Inclusion criteria**: • Male • Elective first time CABG • Left ventricular ejection fraction of at least 40% • Age between 16 and 80 years **Exclusion criteria**: • Serum bilirubin over 50 µmol/L • Serum creatinine over 150 mmol/L • Vital capacity below 40ml/kg • Forced expiratory volume in 1s below 50% predicted • Central nervous system disease • Long-term use of medication acting on the central nervous system • Family history of malignant hyperthermia • Perioperative myocardial infarction	24 cardiac patients were randomised into the two study arms Intervention – n=12 Comparator – n=12 **Patient demographics:** Intervention: • Mean age = 63 • Mean weight = 74kg • Mean height = 165.8cm Comparator: • Mean age = 65 • Mean weight = 75kg • Mean height = 166.5cm ● (Green)	The reported outcomes include: • Ramsay sedation score • Time to extubation • Time to follow verbal command • Mobilization from bed • SCCU length of stay • Hospital length of Stay • Cardiac markers ● (Green)	Study limited to male patients Statistical test results were only reported using the $p<0.05$ threshold; no exact p-values reported. Not UK/NHS setting Midazolam is not the sedative of choice in the UK for the adult population. No conflict of interest and funding information was provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Onset of withdrawal syndrome • Delirium **Procedure**: Patients after CABG were managed with one of two sedation regimes: AnaConDa delivered isoflurane targeted to an end-tidal concentration of 0.5%(1.0-3.5ml/h). Midazolam was delivered at a dose of 0.02-0.03 mg/kg/h (with additional 0.02 mg/kg bolus administered as necessary). This was started after patients reached a Ramsey score of 4 after operative anaesthesia, and sedation was targeted to maintain a Ramsay score of 3-4. Study duration was 24h, after which, if necessary, sedation continued according to standard unit practice. Isoflurane was administered at 1.0-3.5 ml/h and midazolam was initiated at 0.02-0.03 mg/kg/h and adjusted as required. **Statistical analysis:** Between group differences were assessed via Student's t-test or Chi square test. Changes across time were measured with a repeated measures ANOVA; $p<0.05$ was considered significant. **Status:** Published **Funding:** None reported.			No link to an online version of this publication is available

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Conflicts of Interest: None reported ● (Green)			
Rohm (2008) **Location:** Germany **Setting:** ICU	RCT investigating the impact of volatile anaesthetics on post CABG surgery patients Intervention: AnaConDa (sevoflurane) Comparator: IV propofol **Inclusion criteria**: • CABG surgery • 18-80 years • 50-120kg • American Society of Anesthesiologists physical status classification I-III **Exclusion criteria**: • Ejection fraction <30% • Serum creatinine >140 µmol/L • Dialysis • Severe respiratory impairment • Muscle disease • Familial history of malignant hyperthermia • Central nervous disease	70 cardiac patients were randomised into the two study arms Intervention – n=35 Comparator – n=35 **Patient demographics** Intervention • Mean age - 64.6 years • Mean height- 171.7cm • Mean weight -82kg • Male – n=28 (80%) Comparator: • Mean age – 66.4 years • Male – n= 25 (71%) • Mean height – 169.5cm • Mean weight – 82kg ● (Green)	• Sedation length • Ventilator time • ICU length of stay • Hospital length of stay • Adverse events • Bispectral index values ● (Green)	Study outcomes differ from those stated in the trial registration information. Not UK/NHS setting No conflict of interest information was provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Psychiatric disorders • Hepatic impairment • Alcohol or drug abuse • Allergy to study agents **Procedure**: Mechanically ventilated patients were sedated with one of two regimes: • AnaConDa delivered sevoflurane to an end-tidal concentration of 0.5%-1% and piritramide or • IV propofol 2-4 mg/kg/h and piritramide. Sedation was targeted to a RASS score of -4 to -3 and BIS 55-70. Recovery profile was evaluated as time from termination of sedation to spontaneous eye opening, hand grip, following commands (looking to left/right side, showing tongue) and extubation. After extubation patients were evaluated every 15min for 2h and thereafter every 30min. Patients were mechanically ventilated for less than 24h. **Statistical analysis:** Data was assessed with the Kolmogorov-Smirnov test for normality. Demographic data was assessed with the Student's t-test. Other data was analysed via ANOVA, Wilcoxon Rank Sum test or Fisher's exact test; $p<0.05$ was considered significant. The study was powered to detect a 40% decrease in extubation time.			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Status: Published **Funding:** Hospital and department sources of the Klinikum Ludwigshafen, Germany. **Conflicts of Interest:** None reported ● (Green)			
Rohm (2009) **Location:** Germany **Setting:** ICU	RCT looking at renal integrity in postoperative patients sedated with sevoflurane. Intervention: AnaConDa (sevoflurane) Comparator: IV propofol **Inclusion criteria**: See above (Rohm, 2008), but rather than CABG surgery, this study included major abdominal, vascular thoracic surgery patients. **Exclusion criteria**: See above (Rohm, 2008) **Procedure**: Mechanically ventilated patients were sedated with one of two regimes:	Initially 130 patients (1 patient in the sevoflurane arm and 2 in the propofol arm did not receive the allocated treatment and two propofol patients were lost to follow up. Intervention – n=64 Comparator – n = 61 **Patient demographics** Intervention: • Mean age = 67 • Mean weight = 78kg | • Male - n = 46 (72%) Comparator: • Mean age = 67	• Length of ICU and hospital stay • Sedation time • Sedative use • Time on ventilator • /adverse events • Renal function parameters ● (Green)	Note this study had the same clinical trials registration number as Rohm (2008) above. Not UK/NHS setting. No conflict of interest and funding information was provided.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• AnaConDa delivered sevoflurane to an end-tidal concentration of 0.5%-1% and piritramide or; • IV propofol 2 mg/kg/h and adjusted to a RASS score of -4 to -3 and piritramide. Patients were sedated on ICU for less than 24h. Biological specimens for analysis were collected before anaesthesia, at the end of surgery, 24h and 48h after surgery. **Statistical analysis:** See Rohm (2008). Additionally, Bonferroni correction was applied to multiple comparisons. Correlations were assessed with Spearman's rho and Kendall's tau tests. See EAC comment, but authors state that sample size was calculated to detect a 50% difference in alfa-glutathione S-transferase. **Status:** Published **Funding:** None reported **Conflicts of Interest:** None reported ● (Green)	• Mean weight = 80kg • Male – n=44 (72%) ● (Green)		
Hellstrom (2011)	RCT comparing propofol sedation with sevoflurane sedation delivered via AnaConDa.	107 patients were recruited and after exclusions 100 patients randomised to undergo ICU	The reported primary outcome was cTnT	Outcomes differ slightly than those

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Location: Sweden **Setting**: ICU	Intervention: AnaConDa (sevoflurane) Comparator: IV propofol **Inclusion criteria** • Patients undergoing coronary artery bypass grafting (CABG) **Exclusion criteria** • Off-pump CABG • Additional surgery beyond CABG • Need for circulatory support due to perioperative myocardial failure **Procedure:** After chest closure all patients were randomised, via sealed envelope, to one of two sedation regimes: • Sevoflurane was initiated at 2-6ml/h adjusted by 10-20% as needed, with 0.5ml boluses given to deepen sedation; end-tidal concentration was aimed at 0.5%-1.0%. • Propofol was initially administered at 2mg/kg/h adjusted by 10-20% as needed, with 20-50mg boluses given to deepen sedation. Sedation aimed to achieve a Motor Activity Assessment Scale score of 2-3 for a minimum of 2h and until extubation criteria were met at which point the sedatives were removed. Postoperative pain was treated with	sedation with either propofol or sevoflurane via AnaConDa. Intervention – n=50 Comparator – n = 50 **Patient demographics** Intervention**:** • Mean age= 65 years • Male – n= 38 (76%) Comparator: • Mean age – 66 years • Male – n=42 (84%) ● (Green)	levels 12h post-surgery Other reported outcomes (all from 12 hours postoperatively) were: • Cardiac markers • Blood gases ● (Green)	stated in the trial registry information All outcomes reported in the manuscript were for the first 12h post-operative period only. Not UK/NHS setting.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	morphine and paracetamol. Blood samples for biochemical markers were taken at on the ward before surgery and 12h post ICU admission. Blood gas samples were taken in the operating theatre and in ICU. **Statistical analysis:** Sample size was calculated to detect a cTnT difference of 0.1µg/L [80% power; alpha = 0.05] with SD 0.17 µg/L i.e. 50 patients in each group with attrition planned for. Outcomes were analysed using Student's t-test for continuous parameters, with the Mann–Whitney U-test for non-normal data and Fisher's exact test for dichotomous outcomes. **Status**: Published **Funding:** • The regional agreement on medical training and clinical research (ALF [sic]) between Stockholm County Council and Karolinska Institutet • Lena and Per Sjoberg scholarship • Abbott Scandinavia AB sponsored the purchase of sevoflurane (Sevoranes) • Sedana Medical AB supplied the AnaConDa. **Conflicts of Interest:** one author received honoraria as a lecturer for Abbott Scandinavia AB and is an Advisory Board participant for Baxter International Inc. No other conflicts of interest were declared			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	● (Green)			
Mesnil (2011) **Location:** France **Setting:** ICU	RCT comparing sevoflurane and propofol or midazolam over 24h sedation Intervention: AnaConDa with sevoflurane at an end tidal concentration of 0.5% Comparator 1: IV propofol 2% at 2mg/kg/hr Comparator 2: IV midazolam at 0.1 ml/kg/hr **Inclusion criteria**: • 18-80 years • 50-120kg • More than 24h sedation **Exclusion criteria**: • Sedation started more than 6h before inclusion • Septic, haemorrhagic or cardiogenic shock • Head trauma • Glasgow comma scale score < 9 • Pregnancy • Breast feeding • Acute bleeding • Pre-existing neurological disease with consciousness disorder • Familial history of malignant hyperthermia • Chronic renal failure • Child classification C stage cirrhosis	60 patients were initially randomised, with 47analysed Intervention – n=19 Comparator 1 – n=14 Comparator 2 – n=14 **Patient demographics** (for the 47 patients) Intervention: • Median age = 52 years • Male = 53% • Median BMI = 25 Comparator 1 • Median age – 54 years • Male – n = 64% • Median BMI - 26 Comparator 2 • Median age – 55 years • Male – n = 71% • Median BMI - 25 ● (Green)	• Time per day with Ramsay score 3-4 • Blood gases • Sedation duration • Ventilation duration • ICU length of stay • Wake-up time • Extubation time • Remifentanyl and morphine consumption • Patient awakening quality • Adverse events ● (Green)	Not UK/NHS setting Midazolam is not the sedative of choice in the UK for the adult population.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Severe cardiac impairment • Cardiac rhythm disorder **Procedure**: Mechanically ventilated patients received one of three sedation strategies targeted to a Ramsay sedation scale score of 3-4; AnaConDa delivered sevoflurane with IV remifentanil, IV propofol and remifentanil or IV midazolam and remifentanil. In patients over 65 years old, remifentanil, propofol and midazolam does were reduced by 30%. Analgesia and sedation scores were assessed hourly. Wake-up and extubation times were measured from termination of sedation. Patents sedated for >96h were continued on IV sedation. Plasma inorganic fluoride was measured on mornings for the first 4 days. Blood biochemistry was measured on first, second, third and fifth days. Consumption of sedatives and remifentanil were calculated daily. **Statistical analysis** Chi square test, Fisher test, ANOVA and Kruskall-Wallis tests were performed depending on sample size and data distribution; $p<0.05$ was considered significant. Bonferroni correction was applied for 2 by 2 comparisons. **Status:** Published **Funding:** From 'institutional sources'.			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Conflicts of Interest: Disclosed – none reported ● (Green)			
Steurer (2012) **Location:** Switzerland **Setting:** ICU **Date:** October 2007 to September 2009	RCT investigating the impact of volatile anaesthetics on post-surgery cardiac injury markers. Intervention: AnaConDa (sevoflurane) Comparator: IV propofol **Inclusion criteria**: • 18-90 year old • Undergoing elective cardiac surgery requiring extracorporeal circulation • Minimum duration of sedation 4 hours **Exclusion criteria**: • Ejection fraction <30% • Significant coronary impairment • Emergency procedures • Previous cardiac surgery • Chronic pulmonary disease • Renal dysfunction • Insulin dependent diabetes • Pregnancy • Steroid treatment	117 post-cardiac surgery patients were recruited and randomised; after excluding 7 early extubated patients and 4 sedation problem (switched to comparator) patients from the intervention arm and 4 early extubation patients from the comparator arm, 102 patients were analysed. Intervention – n= 46 Comparator – n=56 **Patient demographics** (from the 102 patients)**:** Intervention: • Mean age = 63 years • Male – n =32 (69%) • Mean BMI = 26.6 | Comparator: • Mean age = 64 years • Male – n = 38 (67%) • Mean BMI – 27.1	• Cardiac markers • Blood gases • Pulmonary complication incidence • ICU length of stay • Hospital length of stay ● (Green)	Per-protocol analysis. Not UK/NHS setting.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Procedure: Post-surgery patients receiving invasive ventilation were sedated with either AnaConDa delivered sevoflurane titrated to a MAC of 0.5% with 0.05-0.2 µg/kg/min remifentanil as required, or 0.5-4.0 mg/kg/h propofol with 0.05-0.2 µg/kg/min remifentanil as required. All biochemical markers were assessed for baseline at ICU admission, the 4h after and on the next day. Biochemical markers were assessed on ICU arrival, 4h after initiating ICU sedation and on the morning of postoperative day 1. Blood gases were assessed after 4h sedation/before extubation and on postoperative day 1. Extracorporeal circulation time, aortic cross-clamp time and administration of blood products were recorded to control for confounders. **Statistical analysis:** Study was powered to detect a 0.3 U/l difference between groups in troponin levels. For continuous outcomes linear regression analysis was used, for dichotomous outcomes logistic regression as utilised. Two pieces of regression analysis were undertaken: an unadjusted one and one adjusting for multiple clinical variables. Statistical significance is given only for the $p<0.05$ threshold, but 95% CI are given for the differences between intervention with the comparator being the reference value. **Status:** Published	(Green)		

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Funding: Study received funding from Abbott AG, Baar, Switzerland. **Conflicts of Interest:** The authors declared no conflict of interest, but one author noted receipt of previous grants from the funder of this study ● (Green)			
Hellstrom (2012) **Location**: Sweden **Setting**: ICU	See Hellstrom (2011) above. **Additional Methodological notes:** Sub-study within Hellstrom (2011) focused on the effects of sedative choice on awakening and ICU memories. Memory assessment was done on day of discharge not a set timepoint post-surgery. Adverse events were recorded for the first 12h post-extubation. Statistical power was calculated specifically for this sub-study for a 5-minute difference in wake-up time. ● (Green)	See Hellstrom (2011) above, but note that one patient was excluded from the sevoflurane arm. Additional demographics are presented below Intervention (n=49): • Average age =65 years • BMI = 28.8 • Male – n = 37 (76%) Comparator (n=50): • Average age = 66 years • BMI – 27.3 • Male – n = 42 (84%) ● (Green)	• Time to extubation • Time to adequate verbal response • Adverse recovery events • ICU Memory Tool results • ICU length of stay • Hospital length of stay ● (Green)	See Hellstrom (2011), for note on trial registration outcomes. Power calculation only completed for the wake-up time Short ICU sedation period, with propofol group being sedated for longer. Hellstrom (2011) performed an intention to treat analysis, here a per

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
				protocol analysis was carried out 4 comparator arm patents and 6 intervention arm patients were lost to follow-up for ICU Memory Tool results. Not UK/NHS setting.
Soro (2012) **Location:** Spain **Setting:** ICU **Date:** June 2006- June 2007	RCT investigating the impact of volatile anaesthetics on post-surgery cardiac injury markers. Intervention: AnaConDa (sevoflurane) Comparator: IV propofol **Inclusion criteria**: • 18 years or older • CABG surgery • Required 4 hours sedation **Exclusion criteria**: • Reintervention	75 post-surgery cardiac patients Intervention – n=36 Comparator – n=37 **Patient demographics** Intervention • Mean age = 68.3 • Men = 75% • Mean weight = 74.2kg • Mean height = 164.4 cm • Mean BMI = 27.4	• cTnI • Cardiac markers • Haemodynamic variables • ICU length of stay • Hospital length of stay ● (Green)	Study tried to blind the assessors as to the type of sedation a patient received. It is uncertain how effective this methodology was or whether the placebos given where completely inert with respect to

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Combined surgery • Valve dysfunction • Preoperative cardiac troponin I (cTnI) above 0.5 ng/ml • Altered liver biomarkers • Kidney dysfunction • Chronic alcoholism • Neurological disease **Procedure**: During the non-cardiopulmonary bypass phase of the surgery and in the postoperative period patients received one of two sedation regimes: • Intervention: AnaConDa administered sevoflurane (0.7%-1.5% end-tidal concentration) with IV 10% lipid emulsion (placebo) and remifentanil (0.25-1 ug/kg/min operatively and 0.1-0.5 ug/kg/min postoperatively) • Comparator: AnaConDa administered isotonic saline (placebo) with IV propofol (4-10 mg/kg/h operatively and 1-4 mg/kg/h operatively) and remifentanil (0.25-1 ug/kg/min operatively and 0.1-0.5 ug/kg/min postoperatively) Preoperative blood samples were collected either on the day of surgery or one day before surgery. On the ICU they were collected 6hrs after cardiopulmonary bypass as well as 12h, 24h, 48h and 72h postoperatively. Haemodynamic parameters were assessed before	Comparator: • Mean age = 69.4 • Men = 81.1% • Mean weight = 78.9kg • Mean height = 165.2 cm • Mean BMI = 28.9 ● (Green)		the outcomes assessed. Not UK/NHS setting Random allocation by sealed envelope.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	cardiopulmonary bypass, at the end of surgery, on ICU admission and 6h, 12h, 24h, 48h and 72h thereafter. Length of hospital stay was calculated from ICU admission until the patient met the criteria for discharge. **Statistical analysis:** Sample size was calculated to detect a cTnI difference at 24h with a difference of 2ng/ml considered clinically significant. Shapiro-Wilkes test was used to assess data distribution and Levene's test was used for the assessment of variance homogeneity. Chi-square, McNemar, Student's t-test and Mann-Whitney U-test was used for hypothesis testing. A generalised linear model, with Tukey-Kramer post-hoc analysis, was used to assess the evolution of variables in the two groups. **Status:** Published **Funding:** Disclosed – none reported **Conflicts of Interest:** Disclosed – none reported ● (Green)			
Guerrero Orriach 2013 **Location:** Spain	RCT comparing intra and post-operative sevoflurane/sevoflurane (SS), sevoflurane/propofol (SP) and propofol/propofol (PP).	60 cardiac patients were randomised to either intraoperative sevoflurane or propofol before surgery	• Neurological outcomes • Haemodynamic outcomes • Cardiac markers	Not UK setting

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Setting: Not reported **Date:** Not reported	**Intervention**: AnaConDa - Intraoperative sevoflurane with postoperative sevoflurane or propofol (SS and SP) **Comparator: I**ntraoperative propofol with postoperative propofol (PP) **Inclusion criteria:** • CABG without pump • Level of perioperative risk according to Euroscore scale <7 (in low-moderate risk patients) **Exclusion criteria:** • History of adverse reaction to anaesthetic drugs • Euroscore >7 (in moderate to high risk) • Combined surgery (associated with valve repair or carotid) • Patients with haemodynamic instability, heart failure or need for vasoactive or inotropic drugs before surgery • Emergency surgery **Procedure:** In all groups, anaesthesia was induced using etomidate, fentanyl and cisatracurium. In the SS and SP groups, anaesthesia was maintained using sevoflurane between 0.7 and 1 minimum alveolar concentration (MAC). In the PP group a target-controlled infusion of propofol was used aiming at plasma concentrations of 2 to 4 µg/mL	• SS – n =20 • SP – n =20 • PP – n=20 **Patient demographics** SS • Age range – 61-73 years • Male – n=9 (45%) • Median Euroscore – 5 SP • Age range – 64-71 years • Male – n=10 (50%) • Median Euroscore - 4 PP • Age range – 62-74 years • Male – n=10 (50%) • Median Euroscore – 4 ● (Green)	● (Green)	

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Following surgery in the ICU sedation was given as follows: • SS group: patients were sedated using AnaConda with sevoflurane and end tidal concentration 0.5%-0.7% to achieve BIS between 60 and 70. • SP group: patients were sedated using IV propofol to achieve plasma concentration of 1-1.5 µg/kg/ml and BIS values of between 60 and 70. • PP group: patients were sedated using IV propofol to achieve plasma concentration of 1-1.5 µg/kg/ml and BIS values of between 60 and 70. Data were collected intraoperatively, on arrival at ICU and at 6, 12, 24 and 48 hours postoperatively. **Statistical analysis** Sample size calculation aimed to detect a difference in levels of troponin I of 0.92 ng/mL and a difference in the value of NT-proBNP between groups of 600 pg/mL with statistical power of 0.8 and an α significance level of 0.05. This required 20 patients per group. Epidemiological characteristics of participants were analysed using Fisher Exact test and 1-way ANOVA. Analysis of haemodynamic and biochemical parameters was performed using repeated measures ANOVA and post-hoc analysis using the Bonferroni-Dunn test. **Status**: Published			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Funding: Disclosed – none reported **Conflicts of interest**: Disclosed – none reported ● (Green)			
Marcos-Vidal (2014) **Location:** Spain **Setting:** ICU	Prospective study with sequentially assigned patients comparing sevoflurane and propofol sedation. Intervention: AnaConDa (sevoflurane) Comparator: IV Propofol **Inclusion criteria**: • Patients undergoing cardiac surgery with cardiopulmonary bypass • Over 18 years old • Minimum sedation period of 120min **Exclusion criteria**: • History of malignant hyperthermia • Propofol allergy • Urgent surgery • Cryoablation surgery • Preoperative creatinine level higher than 1.5mg/dL **Procedure**:	144 patients initially enrolled, with 15 patient excluded due high preoperative creatinine levels, cryoablation or urgent surgery. 129 patients were in the final analysis. Intervention – n = 67 Comparator – n = 62 **Patient demographics** Intervention • Mean age = 69.13 • Male = 77.6% • Average BMI = 28.05 Comparator • Mean age = 69.24 • Male = 67.7% • Average BMI = 27.70	The reported outcomes include: The primary outcome was changes in cardiac Troponin T (cTnT) levels. Other reported outcomes include: • Use of cardiovascular support drugs • Incidence of ICU atrial fibrillation • Duration of sedation • Duration of ICU and hospital stay	The phrasing in the manuscripts and figures makes it difficult to interpret what the authors mean in some instances. In the manuscript the table description of hospital length of stay is at odds with how it is described on page 39 of the manuscript. Similarly, there seem to be some typo/grammar issues with how outcomes are

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	After cardiac surgery patients were invasively ventilated and received either: • AnaConDa delivered sevoflurane to achieve end-tidal concentration of 0.5-1%; • IV propofol at 2 mg/kg/h with loading dose of 1mg/kg/h In both groups the target bispectral index score was 60-80 (units not stated), with 0.05-0.1 µg/kg/min remifentanil. Biochemical markers were assed at 4h, 12h, 24h and 48h post ICU admission, except for creatinine which was assessed before surgery (at admission to hospital) as well as 4h, 12h and 24h after ICU admission. **Statistical analysis:** Sample size was calculated to detect a difference of 0.5 ug/l in cTnT levels. Normal distribution was assessed using the Kolmogrov-Smirnov test. Hypothesis testing was carried out using Student's t-tests and Chi-square test. **Status:** Published **Funding:** Disclosed – none reported **Conflicts of Interest:** Disclosed – none reported ● (Green)	● (Green)	• Creatinine, creatinine kinase (CK) and creatinine kinase myocardial band (CKMB) fraction levels ● (Green)	described in Table 3. Not UK/NHS setting

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Jerath 2015 **Location**: Canada and India **Setting**: Cardiovascular ICU **Date**: September 2009 – August 2011	Open label, prospective RCT to evaluate the differences in both cardiac and non-cardiac outcomes in a group of cardiac surgical patients using either volatile anaesthetics (isoflurane or sevoflurane) or IV propofol Intervention: AnaConDa (isoflurane or sevoflurane) Comparator: IV propofol **Inclusion criteria:** • Undergoing elective CABG surgery • Good left or mildly impaired ventricular systolic function (ejection fraction >40%) **Exclusion criteria:** • History of malignant hyperthermia • Propofol infusion syndrome • Severe liver or kidney dysfunction **Procedure**: Patients were randomised to receive either: • AnaConDa group: volatile anaesthetics via AnaConDa with choice of volatile agent left to the discretion of the attending anaesthesiologist.; • IV propofol group: anaesthesia consisted of 5µg/kg fentanyl, 0.05-0.1mg/kg midazolam, 1mg/kg propofol and 0.5mg/kg rocuronium.	141 patients undergoing coronary artery bypass graft (CABG) surgery with normal or mildly reduced left ventricular systolic function were randomised to either receive isoflurane or sevoflurane via AnaConDa or IV propofol Intervention – n=67 Comparator – n=74 **Patient demographics:** Intervention: • Mean age – 65 years • Male – n=61 (91%) • Mean BMI – 28.3 Comparator: • Mean age – 63 years • Male – n=70 (95%) • Mean BMI – 29.9 ● (Green)	• Readiness to extubation time • Extubation time • Cardiac markers • Opioid consumption • Sedation score • ICU length of stay ● (Green)	Not UK setting

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Intraoperative depth of anaesthesia was monitored and adjusted to a BIS of 40-60. **Statistical analysis:** Categorical variables were described as frequencies and analysed using the Fisher exact test. Continuous data were reported using mean (SD) and median (Interquartile range) and analysed using the Wilcoxon rank sum test. **Status:** Published **Funding:** States study was not funded by Sedana Medical **Conflicts of interest:** The authors declared conflicts of interest but none of these related to AnaConDa or Sedana Medical. ● (Green)			
Bellgardt (2016) **Location**: Germany	Retrospective cohort study comparing isoflurane with propofol/midazolam sedation. Intervention: AnaConDa (isoflurane) Comparator: IV propofol or midazolam	200 patients in the final study population from an initial cohort of 369 patients, with 46 patients excluded due to mixed sedation, 103 fell outside the age criteria and 20 were lost to follow-up	Primary outcome: in-hospital mortality Secondary outcome: 365-day mortality after first admission to ICU.	Retrospective/non-randomised study character. IV arm is mixed propofol and

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Setting: ICU **Date**: 2005-2010	**Inclusion criteria**: • Postoperative patients • Ventilated for over 96 hours **Exclusion criteria**: • Over the age of 79 • Under the age of 40 • Received mixed sedation • Lost to follow-up **Procedure**: Patients invasively ventilated who received either: • Isoflurane sedation via the AnaConDa (classic), started within 72h of commencement of ventilation, targeted for an end-tidal concentration of 0.3-0.8% • IV propofol (2-4 mg/kg/h) with later midazolam (0.05-0.2 mg/kg/h) sedation Patients were followed up for 365 days. **Statistical analysis:** Data were analysed using Fisher's exact test, Chi-square test, Student's t-test or Welch's t-test; p=/<0.05 was considered significant. Logistic regression was used to calculate odds ratios. Variables with a positive correlation of 0.3 on Pearson or Spearman correlation analysis were excluded. Goodness of fit was assessed using Hosmer-Lemeshow test and Kaplan-Meier	Intervention: n= 72 Comparator: n = 128 **Patient demographics** Intervention • Male = 46% • Mean age = 66.4 Comparator • Male = 38% • Mean age = 67.7 ● (Green)	Other reported outcomes: • Invasive ventilation duration • Ventilator free days at 30 and 60 days • Lengths of ICU and hospital stay as well as hospital-free days at 90 and 180 days • Laboratory results • ICU admissions • Complication (pneumonia, peritonitis, sepsis, thrombosis/embolism, stroke, acute renal failure, mass bleeding) ● (Amber)	midazolam. Midazolam is not the sedative of choice in the UK for the adult population. The study also reported some outcomes for patients who received mixed sedation. The study reports a comprehensive list of complications but due to lack of detail it was not possible to classify them according to the Clavien-Dindo system. There was no statistically significant difference in the frequency of these complications

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	approach with a log-rank test was used to compare survival. **Status:** Published **Funding:** Disclosed – none reported **Conflicts of Interest:** Disclosed – none reported ● (Green)			between both groups. Not UK setting
Jabaudon 2017 **Location:** France **Setting:** Three ICU's from a French University hospital **Date:** April 2014 - February 2016	Parallel, open label single centre RCT to assess whether sevoflurane via AnaConDa would improve gas exchange and inflammation in acute respiratory distress syndrome (ARDS) compared to midazolam. **Intervention**: AnaConDa (sevoflurane) **Comparator**: IV midazolam **Inclusion criteria:** • Patients with moderate to severe ARDS within 24 hours of onset **Exclusion criteria:** • <18 years of age • Suspected or proven intracranial hypertension • Allergy to midazolam, sevoflurane or cisatracurium	50 patients were randomised within 24 hours of moderate to severe ARDS onset to receive either IV midazolam or inhaled sevoflurane via AnaConDa for 48 hours Intervention n = 25 Comparator n = 25 **Patient demographics**: Intervention • Mean age – 66 years • Male – n=17 (70%) • Mean BMI – 29.6 Comparator	• pCO_2 • Total ventilation time • ICU length of stay • Adverse events ● (Green)	Not UK setting Midazolam is not the sedative of choice in the UK for the adult population. Conflict of interest information was not provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• V_T (6ml/kg predicted body weight) <250ml • History of malignant hyperthermia • Severe liver failure • Neutropenia (<0.5 x 10^9 neutrophils per litre) • Chemotherapy in the last month **Procedure:** Patients were randomised within 24 hours of ARDS onset to either: ● AnaConDa group: sevoflurane rate was started at 6ml/h and adapted every 15 minutes ● Midazolam group: midazolam rate was started at 0.1mg/kg/hr and modified every hour if needed. Sedation was monitored using the BIS with a target value of 40-50 in all patients. **Statistical analysis:** Student's t-test and Mann-Whitney U tests were used for quantitative variables. Categorical data were compared using chi-square or Fisher exact test. Survival rates were compared between the two groups using chi-square test. Effects of time and sevoflurane on Pa_{O2}/FI_{O2} and ventilatory variables were assessed using two-way repeated ANOVA. **Status**: Published **Funding**: Grants from the Auvergne Regional Council and the French Agence Nationale de la Recherche and	• Mean age – 63 years • Male – n=19 (75%) • Mean BMI – 28.1 ● (Green)		

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	the Direction Generale de l'Offre de Soins. Funders had no influence in study design, conduct and analysis or in the preparation of the article. **Conflicts of interest**: Not reported ● (Green)			
Krannich (2017) **Location**: Germany **Setting:** ICU **Date**: November 2010 - November 2015	Retrospective analysis of patients who have survived cardiac arrest being treated with targeted temperature management (TTM) comparing AnaConDa device to IV sedation Intervention: AnaConDa (isoflurane) Comparator: IV sedation using combination of Midazolam and fentanyl **Inclusion criteria:** ● Patients who had experienced nontraumatic cardiac arrest **Exclusion criteria:** ● None reported **Procedure:** All patients underwent TTM and were maintained at 33°C for 24 hours before slowed rewarming. After admission to ICU patients received either:	432 cardiac arrest survivors who underwent TTM. Intervention: n= 110 Comparator: n = 322 **Patient demographics for matched analysis (n-110 in both groups):** Intervention: ● Mean age – 62.3 years ● Male – n=84 (76.4%) Comparator: ● Mean age – 61.9 years ● Male – n=81 (73.6%) ● (Green)	● Time on ventilator ● Length of ICU stay ● Neurological outcomes ● NSE serum concentration ● Adverse events ● (Green)	Retrospective design Not NHS setting Midazolam is not the sedative of choice in the UK for the adult population. Patient demographics not reported for sample a whole. No funding information was provided

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• AnaConDa group: IV sedation (midazolam, 0.03-0.3 mg/kg/hr and fentanyl, 0.3-3 µg/kg/hr) or; • Comparator group: volatile gas sedation using isoflurane via a ventilator and the AnaConDa device. Isoflurane was adjusted as needed to achieve deep sedation (RASS -5) and end-tidal concentration of 0.5-1.5%. **Statistical analysis:** Analysis was performed between groups using two-tailed students t-test, Wilcoxon-Mann-Whitney U test or Fisher exact test. Additional variable effects were removed by pairwise next neighbour matching using the propensity score method. **Status**: Published **Funding**: Not reported **Conflicts of interest:** One author has received payments from C.R. BARD and Zoll and also funding from Bard medical. Another author has received payments from Philips, CR. BARD, Zoll, Medivance, COVIDIEN, Nonin Medical and a grant from German Heart Foundation. All other authors report no conflicts of interest. ● (Green)			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Meiser (2018) **Location**: Germany **Setting**: ICU **Date**: May 2010-September 2013	Retrospective cohort study comparing isoflurane with propofol/midazolam sedation in ARDS patients. Intervention: AnaConDa (isoflurane) Comparator: IV propofol or midazolam **Inclusion criteria**: • Patients undergoing continuous lateral rotational therapy using Rotorest **Exclusion criteria**: • None reported **Procedure**: Patients suffering from ARDS receiving either: • Intervention: isoflurane sedation via the AnaConDa (classic), targeted for an end-tidal concentration of 0.3-0.8%. In 10 subjects isoflurane was started immediately, in 4 subjects within 24h and in 5 after 24h of rotational therapy initiation. • Comparator: IV propofol or midazolam sedation Data were recorded at isoflurane sedation as well as 6h and 24h after it. **Statistical analysis:**	38 patients were included in the study. Intervention n = 19 Comparator n = 19 **Patient demographics** Intervention: • Male = 74% • Mean age = 48.9 • Mean BMI = 28.3 Comparator: • Male = 63% • Mean age = 56.3 • Mean BMI = 25.0 ● (Green)	The reported outcomes include: • Sedative use • Ventilation parameters/ pulmonary mechanics • Blood gases • RASS score • Cardiovascular parameters • Length of invasive ventilation • Length of patient stay • Mortality during continuous lateral rotational therapy ● (Green)	Isoflurane sedation was available from June 2011. Midazolam is not the sedative of choice in the UK for the adult population. The manuscript does not state the dose range used for IV sedatives, nor does it state whether the same criteria were used to target sedation depth. Evidence limited to patients undergoing continuous lateral rotational therapy.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Hypothesis testing was carried out using Chi-square test, Student's t-test, Welch's t-test. **Status:** Published **Funding:** None reported **Conflicts of Interest:** Meiser declared a relationship with Sedana Medical and Pall Medical. No other conflicts were declared. ● (Green)			Not UK/NHS setting. No funding information was provided
Staudacher (2018) **Location**: Germany **Setting**: ICU **Date**: January 2014 to February 2017	Single centre, retrospective cohort study comparing isoflurane sedation delivered via AnaConDa to propofol sedation in comatose patients with return of spontaneous circulation after cardiopulmonary resuscitation patients undergoing TTM Intervention: AnaConDa (isoflurane) Comparator: IV propofol **Inclusion criteria**: • Patients undergoing temperature management after cardiopulmonary resuscitation (CPR) **Exclusion criteria**: • Survival below 48h	214 patients were included in the study Intervention n = 36 Comparator n = 178 **Patient demographics** Isoflurane: • Median age = 66.6 • Male = 86.1% • BMI = 27.1 Comparator: • Median age = 66.0	Reported outcomes: • Patient survival • Delirium • Mechanical ventilation length • ICU stay • Hospital stay • Time to spontaneous breathing ● (Green)	Significant difference (p=0.028) in patient sex between both arms. Retrospective/non-randomised study. Higher proportion of male patients in the isoflurane group. Propofol arm included patients

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Extracorporeal membrane oxygenation support (ECMO) • Patients with an Impella (heart pump) • Time of CPR unclear or CPR under 1 min **Procedure**: Patients were sedated initially to a RASS score of -5 and later to a score of -1 or -2 using either: • Intervention: isoflurane (aimed for an end-tidal concentration of 0.5-1.0%) delivered via AnaConDa (classic) with sufentanil • Comparator: propofol with sufentanil A core temperature of 33 °C was maintained for 24 h, followed by rewarming at 0.2 °C per hour, except when contraindicated (e.g. due to bleeding) a target of 36°C was used. **Statistical analysis:** Hypothesis testing was carried out using t-test, Fisher's exact test, ANOVA or Mantel-Cox test; p≤0.05 was considered significant. Propensity score matching considered age, gender, CPR duration, in hospital cardiac arrest, targeted temperature management targeting 36 °C, pre-existing pulmonary, kidney, liver or cerebral disease. **Status:** Published	• Male = 68.0% • BMI = 25.5 Additional analysis was carried out on propensity score matched patients (36 from each arm). ● (Green)		from 2014-2017, while isoflurane arm included patients from 2015-2017. For some parameters two different analysis were carried out (e.g. Fisher's exact test and Mantel-Cox test). Not UK/NHS setting. Funding information was not provided.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Funding: None reported **Conflicts of Interest:** 'Any of the authors has a conflict of interest for this publication' ● (Green)			
Turktan (2019) **Location:** Turkey **Setting:** Reanimation Unit **Date:** February 2015 to February 2016	RCT comparing sevoflurane and dexmedetomidine sedation. Intervention: AnaConDa (sevoflurane) Comparator: IV dexmedetomidine **Inclusion criteria**: • American Society of Anesthesiology physical status I-III • 18-65 years old • Requiring short-term sedation (<48h) • Had pulmonary disorders **Exclusion criteria**: • Severe hepatic, pulmonary and renal failure • Pregnancy • History of convulsion/seizure • History of familial malignant hyperthermia • Heart rate below 50 beats/min and mean arterial pressure below 60 mmHg	30 patients split equally into each arm (15 patients each) **Patient demographics**: Intervention: • Male = 60% • Mean age = 45.73 • Mean weight = 72.9kg • Mean height = 162.6cm Comparator: • Male = 80% • Mean age = 47.40 • Mean weight = 75.6kg • Mean height = 161.7cm ● (Green)	The reported outcomes include: • Ventilation parameters/pulmonary mechanics • Blood gasses • Patient sedation and comfort scores ● (Green)	Limited relevant outcomes. Only short-term sedation. Comparator not particularly relevant to the UK setting. Some outcomes were not reported in detail. Not UK/NHS setting.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Lack of indication for sedation **Procedure**: Invasively ventilated patients received one of two sedation regimes: • Intervention: sevoflurane delivered via AnaConDa (classic) titrated to 0.5%-1% end-tidal concentration • Comparator: dexmedetomidine (1µg/kg loading dose and 0.2-0.7 µg/kg/h maintenance) Sedation was assessed using the 7-point Riker Sedation Score. Patient comfort was measured using a 3-point scale evaluating adaptation to mechanical ventilation. **Statistical analysis:** Chi-square test was used for categorical variable analysis. Distribution normality was assessed using the Kolmogorov-Smirnov test, while hypothesis testing was carried out using Student's t-test, Mann-Whitney U test and repeated measures analysis; $p<0.05$ was considered significant. No correction seems to have been performed for multiple parameter testing. **Status:** Published **Funding:** Disclosed – none reported **Conflicts of Interest:** Disclosed – none reported			

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	(Green)			
Jung (2020) **Location:** Korea **Setting:** surgical ICU **Date:** April 2018 to October 2018	Prospective study sevoflurane with a retrospective comparison with propofol in postoperative patients. **Intervention** AnaConDa (sevoflurane) **Comparator** IV propofol **Inclusion criteria**: • Elective head and neck surgery patients receiving a tracheostomy • American Society of Anesthesiology physical status I-III **Exclusion criteria**: • Family history of malignant hyperthermia • Chronic kidney disease • Moderate, severe or chronic liver disease • Pregnancy **Procedure**: Mechanically ventilated patients received one of the following sedation regimes: • AnaConDa delivered sevoflurane with remifentanil (0.1-0.2 ug/kg/min) • Propofol sedation	29 patients were included in this study Intervention: 25 prospective enrolled patients Comparator: 24 retrospective patients. **Patient demographics** Intervention**:** • Median age = 62 • Male = 72% • Median BMI = 23.2 Comparator: • Median age = 61 • Male = 70.8% • Median BMI = 23.3 (Green)	• Sevoflurane use • Remifentanil infusion rate during sedation • ICU and hospital length of stay • Delirium incidence • Fluid balance • Norepinephrine use (Green)	Outcomes largely congruent with those in the trial registration. Not UK/NHS setting

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Sedation was targeted to a RASS score of -2 to -3. **Statistical analysis:** Effective dose was calculated using Dixon's up and down method and the isotonic regression method. Confidence intervals were calculated using bootstrapping. Hypothesis testing was carried out using Student t-test, Mann-Whitney's rank sum test (with Bonferroni correction), chi-square test, or Fisher's test; $p<0.05$ was considered significant. **Status:** Published **Funding:** Korean ministry of science funding to one of the authors **Conflicts of Interest:** ' No potential conflict of interest relevant to this article was reported' ● (Green)			
Foudraine (2021) **Location:** The Netherlands **Setting**:	Retrospective propensity matched study aimed to investigate whether sevoflurane combined with higher TTM could decrease the incidence of delirium when compared with IV anaesthetics with lower TTM. **Intervention**: AnaConDa (sevoflurane) **Comparator:** IV midazolam or propofol	170 out of hospital cardiac arrest patients with ROSC were propensity score-matched based on age and gender Intervention – n=85 Comparator – n = 85	• Incidence of delirium in first 14 days in ICU • Duration of ventilation • ICU length of stay	Different TTM thresholds used for intervention and comparator. This was due to a

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
ICU **Date**: January 2014-October 2019	**Inclusion criteria:** • Non-traumatic out of hospital cardiac arrest and who were comatose (Glasgow coma scale (GCS) <8) on admission to ICU) **Exclusion criteria:** • In-hospital cardiac arrest patients • <18 years old • GCS >8 on admission to ICU **Procedure:** Between January 2014 and July 2016, TTM protocol used a target temperature of 32-34ºC with IV propofol or midazolam. This temperature was maintained for 24 hours before cooling was stopped and patients were rewarmed passively. A GCS score >12 was required before extubation. In July 2016 the new standard for post cardiac arrest TTM was to hit an initial target of 36ºC for the first 24 hours and then below 37.5ºC for the next 48 hours. Simultaneously, sedation changed to sevoflurane via AnaConDa. Sevoflurane was targeted to a MAC of 0.5. Delirium was assessed by a nurse using the confusion assessment method for the intensive care unit (CAM-ICU) on 3 consecutive shifts, if possible.	**Patient demographics:** Intervention: • Mean age – 65.4 years • Male – n=61 (71.8%) • Median time to ROSC – 30.6 minutes Comparator: • Mean age – 65.5 years • Male – n=61 (71.8%) • Median time to ROSC – 29.1 minutes ● (Green)	• Hospital length of stay ● (Green)	change in standard practice. Not UK setting Midazolam is not the sedative of choice in the UK for the adult population.

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Statistical analysis: Propensity scored matched pairs were created according to gender and age. Kaplan Meier curves were created to compare the cumulative incidence of delirium until 14 days after hospitalisation. Multivariate logistic cox regression analysis with corrections for confounding variables including time to return of spontaneous circulation (ROSC), amount of sedative used and lowest body temperature was used to estimate the time-dependant risk for delirium. Students t-test was used to compare normally distributed variables. Mann-Whitney U test was used to compare non-normally distributed variables. Smaller sample sizes were analysed using the Fisher exact test. **Status**: Published **Funding**: Disclosed – none reported **Conflicts of interest**: Disclosed – none reported ● (Green)			
Unpublished evidence				

Study and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
[SED001 trial] **Location**: Germany and Slovenia **Setting**: Not reported	[redacted] (Green)	[redacted] (Green)	[redacted] (Green)	[redacted]

(green) – fully matches the scope; (amber) – partially matches the scope.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

All of the 23 included publications (from 21 original studies) were comparative. The two publications comparing the two AnaConDa versions utilised a crossover design (Bomberg 2018, Marcos-Vidal 2020). Fourteen publications comparing AnaConDa delivered sedation to IV sedation were RCTs (Sackey 2004, Hanafy 2005, Rohm 2008 & 2009, Hellstrom 2011 & 2012, Mesnil 2011, Steurer 2012, Soro 2013, Guerrero Orriach 2013, Jerath 2015, Jabaudon 2017, Turktan 2019, SED001). Of the remaining seven publications, one was a prospective study utilising sequential allocation (Marcos-Vidal 2014), five were retrospective studies (Krannich 2017, Bellgardt 2016, Meiser 2018, Staudacher 2018, Foudraine 2021), while one publication reported data prospectively for the AnaConDa arm but utilised retrospective data for the IV arm (Jung 2020). Only the SED001 study was designed as a non-inferiority study. All studies were conducted in adults and none were carried out in the UK.

Twenty-one publications compared AnaConDa delivered sedation to IV sedation. Two studies compared isoflurane to propofol (Staudacher 2018, SED001). Three studies compared isoflurane to midazolam (Sackey 2004, Hanafy 2005, Krannich 2017). Two compared isoflurane to both propofol and midazolam (Bellgardt 2016, Meiser 2018). Jerath (2015) compared both isoflurane and sevoflurane to propofol. Two studies compared sevoflurane to both propofol and midazolam (Mesnil 2011 and Foudraine 2021). Nine publications compared sevoflurane to propofol (Rohm 2008 and 2009, Hellstrom 2011 and 2012, Steurer 2012, Soro 2012, Guerrero Orriach 2013, Marcos-Vidal 2014, Jung 2020). Jabaudon (2017) compared sevoflurane to midazolam. Turktan (2019) compared sevoflurane to dexmedetomidine.

Nine publications looked at post-cardiac surgery patients (Hanafy 2005, Rohm 2008, Hellstrom 2011 & 2012, Steurer 2012, Soro 2012, Guerrero Orriach 2013, Marcos-Vidal 2014, Jerath 2015), three looked at post-cardiac arrest patients receiving therapeutic temperature management (Krannich 2017,

Staudacher 2018, Foudraine 2021), two looked at ARDS patients (Jabaudon 2017, Meiser 2018), two report on patients with various surgical indications (Rohm 2009, Bellgardt, 2016), one reports specifically on head and neck surgery patients requiring tracheostomy (Jung (2020), one reports on patients with pulmonary disorders (Turktan 2019) and two report on patients with over 12h and 24h sedation requirements respectively (Sackey 2004, Mesnil 2011).

5.2 *Critical appraisal of studies and review of company's critical appraisal*

Table 5 summarises the critical appraisal of the twelve RCT trials, while Table 6 summarises the critical appraisal of the nine other included studies. Most studies were of some concern/medium quality. Most concerns arose from deviations from intended interventions in RCTs and from patient inclusion, small sample size and the retrospective nature of non-RCTs. RCTs were assessed using the Cochrane revised risk of bias tool for randomised trials (Sterne 2019). Other comparative trials were assessed using JBI's checklists for case series (Munn ND) and cohort studies (Moola 2020), as well as the NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (NHLBI). Full appraisals can be found in Appendix B.

Only one study (Soro 2012), tried to blind the assessors as to which intervention the patients received. It did this by applying a 10% lipid emulsion (propofol-placebo) in the AnaConDa arm and an isotonic saline infusion (sevoflurane-placebo) administered into an AnaConDa device in the IV arm. In studies that had a trial registration, the measured outcomes in the publications did not always match those declared on the trial registration. Steurer (2012) was faithful in its reporting to its registration methodology, though this study only reported confidence intervals (CIs) rather than p-values, which makes comparing the data from this trial with other trials more challenging. Rohm (2008 and 2009), did not pre-define subgroup analysis in its registration, which the 2008 publication is indicative of. It also predefined extubation time as the primary outcome which is not reported in the 2009 publication. Hellstrom (2011 & 2012), pre-specified troponin levels as the

primary outcome, which was reported in the 2011 publication but only at 12h post-operatively rather than within the 2-day prespecified period. Similarly, renal function was prespecified to be reported with a week's time frame, but markers were only given for 12h. The study also reported additional, not prespecified outcomes. All studies excluded patients that switched sedation modes from the analysis. This point is particularly relevant for the SED001 trial which was powered to be a non-inferiority trial, yet the outcomes reported by the trial and used in the economic analysis (see section 9)

[redacted]

Importantly, there is large heterogeneity among the studies' patient populations; as noted in section 5.1, studies looked as such diverse patient groups as head and neck surgery patients, cardiac surgery patients, cardiac arrest patients, and patients with respiratory problems. Similarly, studies often differed in how parameters were assessed or in the sedation assessment system used to target sedation. For example, some studies looked at cTnT and others at cTnI as markers of cardiac injury, sedation was assessed in some studies using RASS while in others the Ramsay sedation scores. Additionally, while most studies that reported on patient wake-up times looked at extubation times, they also occasionally used a variety of other assessment modalities such as responding to verbal command; similarly, some studies reporting on length of stay (LOS) in the ICU or in hospital, also reported ICU- or hospital-free days. While this heterogeneity largely reflects the ICU patient population and ICU clinical practice it affects inter-trial comparability.

Table 5: Quality assessment of included RCTs (n= 12), for detailed appraisals see appendix B

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	**Overall risk of bias**
Sackey 2004	Some concern	Low	Low	Low	Some concern	**Some concern**
Hanafy 2005	Low	Some concern	Low	Some concern	Some concern	**High**
Rohm 2008 & 2009*	Low	Some concern	Low	Low	Low	**Some concern**
Hellstrom 2011 & 2012*	Some concern	Low	Low	Low	Low	**Some concern**
Mesnil 2011	Low	High	Low	Low	Some concern	**High**
Soro 2012	Low	Some concern	Low	Low	Low	**Some concern**
Steurer 2012	Low	Low	Low	Low	Some concern	**Some concern**
Guerrero Orriach 2013	Some concern	Some concern	High	Low	Some concern	**High**
Jerath 2015	Some concern	Some concern	Low	Low	Low	**Some concern**
Jabaudon 2017	Some concern	Low	Low	Low	Low	**Some concern**
Turktan 2018	Low	Some concern	Low	Some concern	High	**High**
SED001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* These studies had some issues with respect to differences between the outcomes reported and those listed on the trial registration form.

Table 6: Summary of quality assessment of included non-randomised studies (n=9), for detailed appraisals see appendix B

Study	Study Design	Intervention	EAC Comments Summary	Conclusion
Marcos-Vidal 2014	Cohort	AnaConDa vs IV	Some concerns due to differences in baseline troponin levels	**Medium Quality**
Bellgart 2016	Case Series	AnaConDa vs IV	Some issues relating to measurement and participant inclusion	**Medium Quality**
Bomberg 2018	Cross-Over	AnaConDa-100ml vs AnaConDa-S	No eligibility criteria and small sample size	**Low Quality**
Krannich 2017	Cohort	AnaConDa vs IV	Retrospective	**High Quality**
Meiser 2018	Cohort	AnaConDa vs IV	Small sample, retrospective	**Medium Quality**
Staudacher 2018	Cohort	AnaConDa vs IV	Some concerns around changes in care protocols over time	**Medium Quality**
Jung 2020	Cohort	AnaConDa vs IV	Retrospective	**High Quality**
Marcos-Vidal 2020	Before-After	AnaConDa-100ml vs AnaConDa-S	Small sample	**Medium Quality**
Foudraine 2021	Cohort	AnaConDa vs IV	Some concerns about delirium assessment, retrospective	**Medium Quality**

5.3 *Results from the evidence base*

N.B For the purpose of this section any reference to isoflurane or sevoflurane is with the assumption that it is being delivered via the AnaConDa or AnaConDa-S system. The results have been discussed in relation to the sedatives used as the use of isoflurane is more prevalent in current NHS practice, with propofol being a more relevant comparator to the adult population and midazolam to the paediatric population.

Comparison of AnaConDa versions

The EAC assessed the evidence on whether the previous AnaConDa version and the AnaConDa-S could be regarded as the same intervention. Marcos-Vidal (2020) compared arterial blood gases and Bispectral Index (BIS) values and found no statistically significant difference in patient mean arterial pressure (MAP) values, and while it found one instance of statistically significant difference in BIS values between both device versions, it was not a clinically significant difference. The study found two instances of time point comparisons when the pCO_2 levels were significantly lower when the AnaConDa-S was used compared to the classical AnaConDa. Bomberg

(2018) reported no change in the rate of isoflurane use when either of the devices was used, no significant differences in MAP, heart rate, pCO_2 levels or norepinephrine use. Based on this evidence, the EAC accepts that the two devices can be regarded as a single intervention.

Key Outcomes

Clinical experts were asked to state which outcomes were most relevant, in their opinion, for making a clinical decision of whether they would use the AnaConDa-S. Their collated responses showed that three outcomes were of particular clinical significance: ventilation duration, wake-up time and sedation efficiency (see correspondence log). These key outcomes are discussed below in relation to the type of sedation agents used.

Eleven publications reported ventilation duration (Table 7). Of those comparing isoflurane to propofol or a mixture of propofol and midazolam, three studies (Bellgardt 2016, Meiser 2018, Staudacher, 2018) found no significant difference in ventilation duration between groups. Krannich (2017) showed shorter ventilation duration in patients receiving isoflurane compared to those receiving midazolam in the matched analysis but not when analysing the whole dataset. Of the three studies comparing sevoflurane sedation to propofol, Hellstrom (2012) found no significant difference between the groups, while Rohm (2008 & 2009) found significantly shorter ventilation time in the sevoflurane groups compared to the propofol groups in both studies. Jabaudon (2017) compared sevoflurane with midazolam and found no significant difference between groups. Of the publications reporting mixed propofol and midazolam results Mesnil (2011) found no significant difference between groups, while Foudraine (2012) reported shorter ventilation times in the sevoflurane group compared to the IV group. The SED001 trial reported no significant differences in ventilator duration between the AnaConDa and propofol groups.

Wake-up time was reported in six publications (Table 7), usually as either extubation time (time from stopping the sedative infusion to taking out the endotracheal tube) or time to follow verbal command.

[redacted]

[redacted] Two studies comparing isoflurane to midazolam found extubation time and time to follow verbal commands to be significantly shorter in the isoflurane group (Sackey 2004, Hanafy 2005). Jerath (2015), compared both sevoflurane and isoflurane to propofol, and found wake-up time to be faster in the sevoflurane/isoflurane group, for both readiness to extubation and extubation times. Mesnil (2011) compared sevoflurane with propofol and midazolam reported shorter wake-up time and time to extubate in the sevoflurane arm compared to the IV groups. Hellstrom (2012), comparing sevoflurane to propofol, found time to extubation to be significantly shorter in the sevoflurane group.

Table 7: Wake up and ventilation time results

Study	Wake up time (including time to extubation) and ventilation time
Comparative with standard care results	
Sackey (2004)	Wake up time, defined as time to extubation and time to follow verbal command in mins, was significantly shorter in the AnaConDa group compared to the midazolam group (time to extubation 10mins vs 250mins, p<0.001 and time to follow verbal command 10mins vs 130mins, p=0.003). Adjustment for confounders did not diminish the size of observed differences.
Hanafy (2005)	Time to extubation and time to follow verbal command were significantly shorter in the isoflurane (15min and 16min) arm compared to the midazolam arm (120min and 60min); p<0.05 in each case.
Rohm (2008)	Time to extubation was significantly (p<0.001) shorter in the sevoflurane arm (21.5min) compared to the propofol arm (150.5min). Time to recovery was also shorter in the sevoflurane arm when assessed by eye opening (p<0.002), following commands (p<0.002), hand grip (p<0.002) and extubation time (p<0.002). Ventilation time was significantly (p= 0.0001) shorter in the sevoflurane arm (mean 9.0h vs 12.5h).
Rohm (2009)	Ventilation time was shorter in the sevoflurane arm compared to the propofol arm (mean 10.2h vs 13h, p<0.009).
Mesnil (2011)	The wake-up times (not defined how these were assessed) were significantly shorter in the sevoflurane arm compared to both IV arms

	(median 18.6min vs 91.3 min for propofol and 260.2 min for midazolam, p<0.001). Times to extubation were also significantly shorter in the sevoflurane arm compared to both IV arms (median 33.6min vs 326.11min for propofol and 599.62 min for midazolam, p<0.001). Duration of mechanical ventilation was not significantly different between study arms (sevoflurane 51h, propofol 61h, midazolam 58h; p=0.453).
Hellstrom (2012)	Median time to extubating was significantly shorter in sevoflurane patients compared to propofol patients (10 vs 25 minutes, p<0.001). There was no significant difference in ventilation time on ICU (p=0.056; average 185min in the sevoflurane arm and 215min in the propofol arm).
Jerath (2015)	Significantly faster readiness to extubation time was reported for the AnaConDa group compared to the propofol group (mean 135mins vs 215mins respectively, p<0.001). Extubation times were significantly faster in the AnaConDa group compared to the propofol group (mean 182mins vs 292mins respectively, p<0.001)
Bellgardt (2016)	There was no statistically significant difference in ventilation duration between study arms (p=0.17; mean 506h in the isoflurane arm and 431h in the IV arm) or in ventilator-free days at 30 days (p=0.81). There was a statistically significant difference in ventilator-free days between isoflurane and IV groups at 60 days (mean 32.5 days vs 23.2 days, p=0.03)
Jabaudon (2017)	Duration of ventilation did not significantly differ between groups (p=0.3; 12.5 days sevoflurane vs 17.0 days midazolam).
Krannich (2017)	In the overall group analysis, ventilation time was shorter in the AnaConDa group (170 hours) compared to Midazolam (210 hours) but it did not reach statistical significance (p=0.068). In the matched pair analysis, ventilation time was significantly shorter in the AnaConDa group compared to Midazolam (170.5 hours vs 269 hours, p=0.003)
Meiser (2018)	Mean ventilation time in the isoflurane arm was 465h and 618h in the IV arm (p=0.26).
Staudacher (2018)	There was no significant difference in the duration of mechanical ventilation between the study arms before (p=0.344) or after propensity score

	matching (p=0.426). After matching the average duration of mechanical ventilation was 99.0h in the isoflurane arm and 93.1h in the propofol arm.
Foudraine (2021)	Median duration of ventilation was significantly shorter in the sevoflurane via AnaConDa group compared to the IV group (34.3 hr vs 70.3 hours, p=0.001)
Unpublished evidence	
SED001 trial	[redacted]

Nine publications reported on sedation efficiency (Table 8). For studies comparing isoflurane to propofol, [redacted] Staudacher (2018) reported no significant difference between the groups in time to spontaneous ventilation before or after matching. While the isoflurane arm had a significantly lower use of sufentanil it had a significantly higher use of norepinephrine. None of the studies comparing isoflurane to midazolam reported any significant difference (Sackey 2004, Hanafy 2005). Meiser (2018), compared isoflurane to both IV agents and reported significantly better sedation efficiency in the isoflurane group at 6h and 24h and lower opioid use at 6h and 24h compared to the IV group. isoflurane patients also spent a significantly higher proportion of time breathing spontaneously while in deep sedation compared to the IV patients at 6h and at 24h. In studies comparing sevoflurane to propofol, three reported no significant difference between the study arms (Rohm 2008 & 2009, Marcos-Vidal 2014, Jung 2020). Mesnil (2011), who compared sevoflurane to both IV agents, reported no significant difference in sedation duration, time spent in target sedation range or in the remifentanil infusion rates between groups.

Table 8: Sedation efficacy results

Study	Sedation efficacy (isoflurane/sevoflurane consumption, opioid use, Bispectral index (BIS), time within desired sedation level)
Device comparison results	
Bomberg (2018)	Patients' sedation level was unaffected by switching between devices. Isoflurane rate remained unchanged during the use of both devices (3.1 +/-2.0ml/h) across the entire observation period of 30 hours. The end-tidal concentrations of isoflurane ranged from 0.2 to 0.8 MAC and were slightly greater with the AnaConDa than with the AnaConDa-S (AnaConDa mean versus AnaConDa-S, 2 h: 0.55±0.18 versus 0.52±0.19 MAC, p=0.015.
Marcos-Vidal (2020)	Sedation objectives were measured using the bi-spectral index (BIS). The only significant difference was between AnaConDa-S at 120 mins and AnaConDa at 30 mins (p-value not stated) but this difference was not considered clinically relevant as values still lay within objective clinical range (66.57 and 58.3 respectively; but note that clinical range is stated as 60-80).
Comparative with standard care results	
Sackey (2004)	Proportion of time within desired sedation level and opioid use were not significantly different between groups (p-values not given; 54% Isoflurane vs 59% midazolam). 5 isoflurane and 6 midazolam patients were close to self-extubation and showed signs of overt agitation (no p-values or further discussion needed).
Hanafy (2005)	There was no significant difference in median Ramsay sedation scores in the first 16h period; p>0.05). There was no significant difference in the amount of sedation boluses or in morphine requirement between both study arms; p>0.05.
Rohm (2008)	There was no statistical difference in sedation length between both the sevoflurane and propofol arms (mean 8.1h and 8.4h respectively; p=0.87). Mean sevoflurane consumption was 3.2+/-1.4 ml/h while mean propofol sedation was 2.4+/- 1.1 mg/kg/h. Piritramide consumption was 7.3 mg (+/-7.2) in the sevoflurane arm vs 7.7 mg (+/- 7.1).
Rohm (2009)	No significant difference in mean sedation time between the sevoflurane group (9.2h) and the propofol group (9.3h; no p-value given). Sevoflurane use was 3.3 ml/h (+/-1.2). Propofol use was 2.1mg/kg/h (+/-0.6) mg/kg/h.

Hellstrom (2011)	Mean sedation dose and time Propofol: 2.0 mg/kg/h for 221min. Sevoflurane: 3.78ml/h (mean end-tidal concentration 0.8%) for 176min (p=0.03).
Mesnil (2011)	Median duration of sedation was not significantly different between groups (p=0.887; 50h sevoflurane vs 57h propofol vs 50h midazolam). There was no significant difference in the time spent in target sedation range (Ramsay Score 3-4) between the groups (p=0.681; 75% sevoflurane vs 75% propofol vs 70% midazolam). But the sevoflurane group received less sedative (p<0.001; 1.5 sevoflurane vs 5 propofol vs 3.5 midazolam) and remifentanil dose modifications (p=0.002; 1.5 sevoflurane vs 4.5 propofol vs 4.5 midazolam), There was no significant difference in the remifentanil infusion rates between the study arms (p=0.962; 9 µg/kg/h sevoflurane vs 12 µg/kg/h propofol vs 10 µg/kg/h midazolam). Mean end-tidal sevoflurane concentration was 0.64%, with initial sevoflurane doses of 2-6ml/h. Initial propofol rate was 2mg/kg/h while initial midazolam rate was 0.1mg/kg/h.
Hellstrom (2012)	Median length of study drug administration was 185 minute for propofol and 165 minutes for sevoflurane (mean times reported in Hellstrom 2011). See above for sedative infusion rates.
Soro (2012)	Postoperative sedation consumption was 1-4mg/kg/h for propofol, but the rate for sevoflurane was not stated.
Steurer (2012)	Propofol consumption was 0.5-4.0 mg/kg/h Sevoflurane rate was not stated.
Marcos-Vidal (2014)	There was no significant difference in sedation duration between both study arms (p= 0.451; 285.82min sevoflurane vs 306.13min propofol). Sevoflurane use was 3-8 ml/h. Propofol use rate was 1-4mg/kg/h.
Bellgardt (2016)	Isoflurane infusion rates were not given. Propofol as first administered at 2-4 mg/kg/h and then midazolam was administered at 0.05-0.2 mg/kg/h.
Meiser (2018)	Isoflurane sedated patients had significantly deeper sedation than IV arm patients at 6h and at 24h following initiation of continuous lateral rotational therapy (p=0.03 and p<0.001 respectively). Opioid use was significantly lower in the isoflurane arm at 6h and at 24h compared to the IV arm (p<0.001 and p<0.001 respectively).

	More patients in the isoflurane arm breathed spontaneously on the deep sedation compared to the IV arm at 6h and at 24h post initiation of continuous lateral rotational therapy. At 6h the values were 63% vs 16% respectively (p=0.003) and the 24h values were 90% and 16% (p<0.001), respectively. Isoflurane was administered at 3-10ml/h (starting rate was 5ml/h). Propofol was started at a rate (mg/kg/h) of 0.83(0.39+/-), and at 6h it was 0.87(+/-0.42) and at 24h it was 0.10(+/-0.46). Midazolam was started at a rate (mg/kg/h) of 0.07(+/-0.03), at 6h it was 0.07(0.03) and at 24h it was 0.10(+/-0.05).
Staudacher (2018)	There was no statistically significant difference in time to spontaneous breathing between the study arms, with median times to spontaneous breathing being 9.3h in the isoflurane group and 9.5h in the propofol group (two p-values were given: p=0.702 and p=0.373). After propensity score matching, the difference between the groups remained non-significant (p=0.553; 9.3h Isoflurane vs 8.2h propofol). There was significantly higher use of norepinephrine (p=0.004) but significantly lower use of sufentanil (p<0.001) in the isoflurane arm when compared to the propofol arm (values available only in charts at 12h intervals following cardiac arrest to 120 h post cardiac arrest). No sedative infusion rates were given.
Turktan (2019)	No detailed results were provided on sedation score and patient comfort assessment. Sevoflurane consumption was reports as 4-10ml/h with an average rate of 5ml/h. Dexmedetomidine infusion was 1 µg/kg in 10 minutes for loading and 0.2-0.7 µg/kg/h for maintenance.
Jung (2020)	The 50% effective dose of sevoflurane was an end-tidal concentration of 0.36% or 40% depending on regression method, while the 95% effective dose was 0.69%. These included concurrent remifentanil administration. Median postoperative sedation in the sevoflurane group was reported as 680min in the text, but as 771 minutes in the table. Median propofol sedation was 1508.2 min (p=0.099). There was no information on the sedative rates used. Sevoflurane arm patients received significantly (p=0.001) less remifentanil (median dose 2.52 µg/kg/hr) than propofol patients (median dose 3.66 µg/kg/hr)
Unpublished evidence	**Unpublished evidence**
SED001 trial	[redacted]

	[redacted]

Additional outcomes

Sixteen publications (Table 9) reported on ICU LOS. Of the studies comparing isoflurane to propofol sedation, Staudacher (2018) found no significant difference in length of ICU stay [redacted]. In the two studies that compared isoflurane to midazolam, one found significantly shorter ICU LOS in the isoflurane group (Hanafy, 2005) and the other found no difference between groups on a whole group level, but in the matched pairs analysis found significantly shorter ICU LOS in the isoflurane group (Krannich 2017). Both studies comparing isoflurane to both IV agents found no significant difference between groups (Bellgardt 2016 and Meiser 2018). Of the two studies comparing sevoflurane to both IV agents, Foudraine (2021) found sevoflurane patients reported significantly shorter ICU stays than the IV patients, while Mesnil (2011) reported no significant difference between groups. All eight publications that compared sevoflurane to propofol reported no significant difference in the length of ICU stays (Rohm 2008 and 2009, Hellstrom 2011 and 2012, Steurer 2012, Soro 2012, Marcos-Vidal 2014, Jung, 2020). Jabaudon (2017), compared sevoflurane to midazolam, and also did not find any significant difference in ICU LOS between groups.

Twelve publications reported on patient hospital LOS (Table 9). None of the four studies comparing isoflurane to propofol or midazolam (or both) found any significant difference between groups (Staudacher 2018, Hanafy 2005, Bellgardt 2016, Meiser 2018). Jerath (2015) compared sevoflurane and isoflurane with propofol and found no significant difference between groups. Foudraine (2021) compared sevoflurane with both midazolam and propofol and found a significantly shorter stay in the sevoflurane group compared to the IV group. Except for Rohm (2008 & 2009), none of the other five studies

comparing sevoflurane to propofol found any significant difference in hospital LOS between groups (Hellstrom 2012, Steurer 2012, Soro 2012, Marcos Vidal 2014, Jung 2020). Both Rohm publications (2008 and 2009) reported the sevoflurane group to have a significantly shorter hospital stay compared to propofol group. These results are important in regards to the economic analysis and therefore additional detail has been added to this results table.

Table 9: ICU and hospital length of stay results

Study	ICU length of stays	Hospital length of stay
Comparative with standard care results		
Hanafy (2005)	There was no significant difference in SCCU stay between the isoflurane and midazolam groups (19hr vs 20hr, no p-value reported).	There was no significant difference in hospital length of stay the isoflurane and midazolam groups (5 days vs 5.5 days, no p-value reported).
Rohm (2008)	There was no significant difference in mean length of ICU stay between the sevoflurane and propofol groups (27.8hr vs 39.6hr, p=0.062).	The mean length of hospital stay was significantly shorter in the sevoflurane group compared to the propofol group. (10.6 days vs 14.0 days, p=0.026)
Rohm (2009)	Mean length of ICU stay was not significantly different and was 30.9h in the sevoflurane arm and 38.8h in the propofol arm (no p-value given).	Mean hospital stay was significantly shorter in the sevoflurane group compared to the propofol group (12.5 days vs 15.8 days, p=0.035).
Hellstrom (2011)	Authors state that there was no statistically significant difference in length of ICU stay between the propofol and sevoflurane patients, but did not show any data.	Not reported.
Mesnil (2011)	Median ICU stay was not significantly different between the sevoflurane, propofol midazolam groups (10days vs 12days vs 12days, p=0.945).	Not reported
Hellstrom (2012)	There was no significant difference in median ICU length of stay between groups (22hr in both study arms, p=0.364), with ten patients in both arms requiring a stay longer than 24h and five patients in both arms requiring a stay longer than 48h.	There was no significant difference in median hospital length of stay between groups (6 days in both groups, p=0.866).
Soro (2012)	There was no significant difference in average ICU length of stay between the sevoflurane and propofol groups (71h vs	here was no significant difference in average hospital length of stay between the sevoflurane and propofol groups (9.2 days vs 9.6 days,

	76h, p=0.771; note only one p-value was given for both outcomes reported in this table).	p=0.771; note only one p-value was given for both outcomes reported in this table).
Steurer (2012)	There was no statistically significant difference in ICU length of stay between sevoflurane and propofol groups (adjusted difference in means of 0.07 days, no p-value given)	There was no statistically significant difference in hospital length of stay between both sevoflurane and propofol groups (adjusted difference in means of -0.2 days, no p-value given).
Marcos-Vidal (2014)	There was no significant difference in length of ICU stay (p=0.625), between the sevoflurane and propofol groups (44.09h vs 46.76h, p=0.625)	The text reports no differences were found between the study arms in the length of hospital stay. It is unclear if data in table 3 refers to this statement. If yes, the mean time from surgery to discharge was 7.53 days in the propofol group and 6.51 days in the sevoflurane group. P=0.117.
Jerath (2015)	There was no significant difference in readiness to ICU discharge between groups (p=0.22) ICU discharge time did not significantly differ between groups (p=0.34)	There was no significant difference in hospital length of stay did not differ significantly between groups (6 days in both groups, p=0.79)
Bellgardt (2016)	There was no significant difference in mean ICU length of stay between isoflurane and IV groups (30 days vs 26 days, p=0.19).	There was no significant difference in mean hospital stay between isoflurane and IV groups (60hr vs 48hr p, p=0.08). There was no significant difference in hospital-free days at 90 days between isoflurane and IV groups (p=0.77), but there was a significant difference at 180 days (62.1 days vs 44.1 days; p=0.04).
Jabaudon (2017)	There was no significant difference in ICU length of stay between sevoflurane and midazolam groups (18 days vs 23 days, p=0.9)	Not reported
Krannich (2017)	In the overall group analysis, there was no significant difference in median ICU stay between isoflurane and IV groups (8days vs11days, p=0.116) In the matched pairs analysis ICU stay was significantly shorter in the AnaConDa group compared to Midazolam (8.5 days vs13 days, p=0.006)	Not reported

Meiser (2018)	There was no significant difference in mean ICU length of stay between isoflurane and IV groups (30 days vs 36 days, p=0.48)	There was no significant difference in mean hospital stay between the isoflurane and IV groups (45 days vs 51 days, p=0.60)
Staudacher (2018)	There was no significant difference in median ICU length of stay between the isoflurane and propofol groups (11.1 days vs 9.8 days, p=0.320)	There was no significant difference in median hospital length of stay between the isoflurane and propofol groups (15.1 days vs 13.1 days, p=0.218)
Jung (2020)	There was no significant difference (in median ICU length of stay between groups (2 days in both groups, p=0.208).	There was no significant difference in median hospital length of stay between sevoflurane and propofol groups, (22.8 days vs 26.4 days, p=0.226).
Foudraine (2021)	Median ICU length of stay was significantly shorter in the sevoflurane group compared to the IV group (2.5 days vs 4.1 days, p=0.001).	Median hospital length of stay was significantly shorter in the sevoflurane group compared to the IV group (5.5 days vs 9.8 days, p=0.04).
Unpublished evidence		
SED001 trial	[redacted]	[redacted]

Eight publications reported on cognitive/neurological outcomes (Table 10). Rohm (2008 & 2009) did not provide statistical analysis of these outcomes, but reported delirium frequency, dream frequency and promptness of orientation. Mesnil (2011) reported significantly better awakening quality in the sevoflurane group compared to the IV group. Hellstrom (2012) reported no significant memory differences between groups (memory tool not specified), while sevoflurane patients responded earlier with reporting their date of birth compared to propofol patients. Krannich (2017), Staudacher (2018) and Jung (2020) reported no significant difference in neurological outcomes between groups with Jung reporting no incidence of delirium at all in their study.

Foudraine (2021) reported a significantly lower incidence of delirium in the sevoflurane group compared to the mixed IV group.

Table 10: Cognitive and neurological results

Study	Cognitive/neurological outcomes
Comparative with standard care results	
Rohm (2008)	Dreams were reported by 5 sevoflurane and 6 propofol patients. One sevoflurane patient reported hallucinations. Orientation was judged prompt in 19 sevoflurane and 17 propofol patients (no p-value given). Delirium was reported in 3 sevoflurane and 4 propofol patients (as reported in text; one more patient was included in each arm in the table).
Rohm (2009)	Delirium was reported in 7.8% sevoflurane and 11.5% propofol patients (no-p value given)
Mesnil (2011)	The study reported significantly better awaking quality (corresponding to a lower score) in the sevoflurane arm (score =1) versus score = 2.5 in the Propofol arm and score = 2 in the Midazolam arm, but did not provide any reference to the scoring system used (p<0.001).
Hellstrom (2012)	Patients in the sevoflurane arm responded earlier with their date of birth than propofol arm patients (p=0.036), but most patients in both arms responded within the first 15 minutes after sedation was stopped (circa 70% of propofol and circa 90% of sevoflurane patients – read from the figure). There were no statistically significant between study arms in the results of the ICU memory tool (group p-values between 0.24 and 1.00).
Krannich (2017)	Using the Pittsburgh Cerebral Performance Category (CPC), good neurological outcome (CPC 1-2) was equal in both groups following sedation: 49/110 in the AnaConDa group and 49/110 in the Midazolam group, p =0.599. There was no significant difference between groups in the number of patients who died or remained in an unresponsive wakefulness syndrome or coma.
Staudacher (2018)	There was no statistically significant difference in the proportion of patients experiencing delirium between groups p=0.569).
Jung (2020)	Authors reported no incidence of delirium in either study arm
Foudraine (2021)	Incidence of delirium was significantly lower in the sevoflurane via AnaConDa group than the IV group (16.1% vs, 37.3%, p=0.001)

Nine studies reported on cardiac, renal and hepatic biochemical markers (Table 11). Hanafy (2005), Rohm (2009), Hellstrom (2011), Mesnil (2011) and Soro (2012) reported no significant differences in these study outcomes. Steurer (2012) found that Sevflurane patients had lower cTnT and CK levels on postoperative day one compared to propofol patients. Guerrero Orriach (2013) found significantly lower levels of troponin I and N-terminal pro-brain natriuretic peptide in the sevoflurane group compared to propofol. Marcos-Vidal (2014) reported significantly lower cTnT levels in the sevoflurane group compared to the propofol group and Bellgardt (2016) reported significantly elevated C-reactive protein levels in the isoflurane group compared to the mixed IV group.

Table 11: Cardiac, renal and hepatic marker results

Study	Cardiac, renal and hepatic markers
Device comparison results	
Bomberg (2018)	Mean arterial pressure, heart rate and norepinephrine dose were not significantly different between devices at any timepoint (p-values not reported)
Marcos-Vidal (2020)	Mean arterial pressure (MAP) did not differ significantly between AnaConDa-S and AnaConDa at any time-point (p =0.871-0.896)
Comparative with standard care results	
Hanafy (2005)	CKMB levels were not significantly different in the two groups; p>0.05.
Rohm (2009)	Inorganic fluoride levels were increased significantly in the sevoflurane arm at 24h and 48h (p<0.001) but not in the propofol arm. Alpha-glutathione S-transferase levels were significantly increased in both arms at 24h and 48h (p<0.008) with no inter-group significant difference (no p-value given). There was no correlation between these levels and fluoride levels (no p-value given).
Hellstrom (2011)	There was no significant statistical difference between treatment groups in 12h post-operative cTnT (p=0.104). The authors reported a less pronounced rise in cTnT levels post-surgery in the sevoflurane group on post hoc analysis

	(p=0.008). No significant statistical difference was found in the levels of the other reported biochemical markers (p- values from 0.24-0.93). No statistically significant difference was found at 12hours post-operatively with respect to mean arterial pressure, heart rate or central venous pressure (no p-values given).
Mesnil (2011)	Sevoflurane patients spent significantly more time with a mean arterial pressure of between 65 and 95 mmHg (p=0.002), while receiving significantly less vasoactive agents (35% vs 48% for propofol and 35% vs 42% for midazolam; p=0.001). The authors reported no significant changes in markers of hepatic or renal toxicity, save lower urea levels in the sevoflurane group on days 3 and 4 (no p-values reported). Mean plasma fluoride level (whole study sample) was 82 µmol/l.
Soro (2012)	There was no significant difference in the levels of cardiac injury biomarkers or haemodynamic variables between both intervention arms except central venous pressure on admission p<0.05. No other p-values reported.
Steurer (2012)	The unadjusted model revealed significant reductions in CK: difference -140 (95% CI = -250 - -30 U/l) and myoglobin: difference -113 (95% CI = -187 - -39 ug/l) levels 4h post ICU admission as well as reduced cTnT: difference -0.4 (95% CI = -0.7 - -0.1 ug/l) and CK: difference -258 (95% CI = -434 - -83 U/l) levels on the postoperative day in the sevoflurane arm compared to the propofol arm. Only postoperative day 1 cTnT (-0.4 - -0.02 ug/l) and CK levels (-331 - -8 U/l) remained significantly different in the adjusted model. No p-values reported
Guerrero Orriach (2013)	Troponin I levels differed significantly between groups at 24 hours; SS vs SP (0.5 vs 1.61, P<0.05), SS vs PP (0.5 vs 2.27, p<0.05) and SP vs PP (1.61 vs 2.27, p<0.05) N-terminal pro-brain natriuretic peptide showed significant between group differences at 24 and 48 hours postoperatively; SS/SP (501 vs 1270, p<0.05), SP/PP (1270 vs 1775, p<0.05) and SS/PP (501 vs 1775, p<0.05). While both time points are highlighted as varying significantly between groups, it is unclear if the values given are for 24h or 48h.
Marcos-Vidal (2014)	cTnT levels were significantly different between study arms at 12h (p=0.026) and 24h (p=0.007) postoperatively, as well as in the difference between cTnT levels (p=0.027) at admission and peak cTnT levels. For the sevoflurane arm they were: • 12h = 0.69 µg/l • 24h = 0.37 µg/l • 48h = 0.37 µg/l • Difference between admission level and peak = 0.51 µg/l

	For the propofol they were: • 12h = 0.89 µg/l • 24h = 0.60 µg/l • 48h = 0.60 µg/l • Difference between admission level and peak = 0.67 µg/l Difference between means (cTnT) at 12 hours (propofol minus sevoflurane): 0.19 (95% CI 0.02-0.34; p=0.026). Difference between means (cTnT) at 48 hours (propofol minus sevoflurane): 0.22 (95% CI 0.06-0.39; p=0.007). There were no significant differences in creatinine, CK and CKMB levels between both study arms at different time points (no p-values given).
Jerath (2015)	Cardiac index scores were significantly higher at ICU admission in the AnaConDa group compared to midazolam (2.9 vs 2.5 respectively, p<0.001). However, by ICU discharge, there was no significant difference between groups (2.5-2.6; p=0.55)
Bellgardt (2016)	The authors report no significant difference between groups in levels of creatinine (p=0.61) and leukocytes (p=0.18). C-reactive protein was significantly elevated in the isoflurane arm compared to the IV arm (p=0.04), with a mean level of 149 mg/l in the isoflurane arm and 118 mg/l in the IV arm.
Jabaudon (2017)	No significant differences were seen between groups for mean arterial pressure or heart rate.
Meiser (2018)	No statistically significant differences were reported in cardiovascular parameters or norepinephrine use between study arms.
Jung (2020)	There was no statistically significant difference in norepinephrine use between both groups (p=0.674 for number of patients receiving it, p=0.379 for infusion time).

Six studies reported on patient blood gas results (Table 12). Hellstrom (2011) reported a significant difference in central venous oxygen saturation at extubation with higher values in the sevoflurane arm. Mesnil (2011) and Mesier (2018) reported no significant difference between study groups in PaO_2/FiO_2 ratios, while Steurer (2012) reported this outcome to be better in the sevoflurane group compared to the propofol group on postoperative day one. Jabaudon (2017) reported significantly better PaO_2/FiO_2 ratios in the sevoflurane group compared to the Midazolam group. Turktan (2019) reported

significantly higher $PaCO_2$ levels at all time points except baseline in the sevoflurane arm compared to the dexmedetomidine arm.

Table 12: Blood gas results

Study	Blood gas analyses
Device comparison results	
Bomberg (2018)	pCO_2 levels were not significantly different between devices at any timepoint (p-values not reported)
Marcos-Vidal (2020)	Partial pressure of carbon dioxide (pCO_2) levels were significantly lower with the AnaConDa-S at 90mins compared to AnaConDa at 30 mins (45.65 and 49.53 respectively, p=0.02) with the same tidal volumes. pCO_2 levels were significantly lower with the AnaConDa-S at 120 mins compared to AnaConDa at 60 mins (40.36 and 44.80 respectively, p=0.001) with the same tidal volumes
Comparative with standard care results	
Hellstrom (2011)	There were no significant differences in central venous oxygen saturation in the sevoflurane and propofol groups at ICU admission (p=0.06). However, there were significant differences before extubation (65% sevoflurane vs 62% propofol p=0.01)
Mesnil (2011)	Median PaO_2/FiO_2 was not significantly different between groups (p=0.856)
Steurer (2012)	There was a significant increase in the PaO_2/FiO_2 ratios on postoperative day one (CI = 2 – 81 mmHg) but not 4h after admission, in the sevoflurane arm when compared to the propofol arm. No p-value given.
Jabaudon (2017)	Arterial oxygenation was assessed using $PaO_2/FI0_2$ ratio. Day 2 mean $PaO_2/FI0_2$ was significantly higher in the sevoflurane with AnaConDa group (205 mmHg) compared to the midazolam group (166 mmHg, p=0.04). Significant differences were also seen at day 3 with sevoflurane ratios being higher (216 mmHg) compared to midazolam (171 mmHg). No significant differences were seen at days 1 or 4. The gain in $PaO_2/FI0_2$ ratio from baseline to day 2 was significantly higher in the sevoflurane with AnaConDa group (95 mmHg) compared to midazolam (50 mmHg, p=0.02). Arterial $PaC0_2$ levels did not differ significantly between groups.

Meiser (2018)	There was no statistically significant difference in the PaO_2/FiO_2 ratio or $PaCO_2$ levels, with no significant differences in ventilator (pressure and volume) settings save for a statistically significant lower pressure difference between end expiratory and inspiratory pressure in the isoflurane group at 24h (p=0.03).
Turktan (2019)	No significant differences were found in ventilation parameters/pulmonary mechanism, pH and PaO_2 levels (p= from 0.98-0.6). Authors report higher $PaCO_2$ and end-tidal CO_2 levels in the sevoflurane arm at all time points (p= from 0.002 to 0.03) except for $PaCO_2$ at baseline (p=0.07).

SED001 Trial

[redacted]

Summary

Out of all the reported outcomes, studies have consistently reported better wake-up times (usually reported as extubation time) in the AnaConDa arms compared to the IV arms. The studies were inconclusive in reference to the

other measured outcomes. Notably, all the included studies looked at different drug combinations and any differences between groups are likely to fundamentally be due to these drug differences as well as the variables involved in patient treatment and are unlikely to be solely attributed to the use of the device.

6 Adverse events

The company submission did not contain any links to adverse incident reports on the MHRA and MAUDE databases. Searches carried out by the EAC revealed no relevant entries in the US Food and Drug Administration MAUDE database. Two reports were identified on the MHRA database. One was dated 9th of August 2006 and highlighted the risk of sedative overdose due to inconsistencies in the instructions for use and user error which have occurred in the past. It stated that the inconsistencies in the instructions were rectified in July 2005 after Sedana Medical took over the manufacturing of the device. The other report is dated 22 January 2020 and pertains to three defective batches of the product that had a dimensional variation resulting in a possible loose-fitting connection on the patient side of the device.

The EAC also compiled a list of adverse events presented in the reviewed evidence base. Table 13 shows the incidents reported in each publication (excluding some of the neurological incidents such as delirium which are presented in the outcome Table 10). To allow for an approximate comparison of their severity the EAC graded them using the Clavien-Dindo scale (Dindo 2004, Hebert 2021). The meaning of Clavien-Dindo scale categories is briefly outlined below:

- Grade I: Any deviation from normal postoperative management course, not including surgical / endoscopic / radiological interventions and most pharmacological interventions

- Grade II: Patient requires pharmacological treatment, save for those falling under Grade I

- Grade IIIa: Patient requires surgical / endoscopic / radiological not under general anaesthesia
- Grade IIIb: Patient requires surgical / endoscopic / radiological under general anaesthesia
- Grade IV: Life-threatening complications requiring ICU-level management
- Grade V: Death

The EAC reiterates that ICU patients are highly complex and as such the majority of adverse events are unlikely to be associated specifically to AnaConDa-S use. Moreover, as mentioned previously, AnaConDa-S utilises different medication to achieve sedation than the comparator and this is likely to bear more weight on the occurrence of many of the mentioned adverse events rather than the AnaConDa-S device itself. Both the clinical experts and the manufacturer (see correspondence log) acknowledge that such a distinction between adverse events relating to the device and the medication should be maintained.

The clinical experts (see correspondence log) have acknowledged that the adverse events linked to the use of AnaConDa-S are likely to be similar to those linked to the use of HMEs. The EAC believes that, regarding the incidents highlighted on the MHRA database, loose fitting connections due manufacturing defect are a potential risk associated with the use of any part of the ventilation circuit. As such, the EAC does not have any safety concerns relating to the use of the AnaConDa-S device.

Table 13: Adverse events reported in the included studies

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Comparison with standard care results						
Sackey (2004)	During sedation, 3 isoflurane and 2 midazolam episodes of hypertension were reported.	None reported.	None reported.	None reported.	One patient in the midazolam group required dialysis during treatment. A further 2 in this group required dialysis within 3 days of study end.	2 patients (1 from the isoflurane and 1 from the midazolam group) died during the study period.
Hanafy (2005)	None reported.	There was 1 incident of hypotension in each study arm and also 1 incident of agitation in each study arm.	None reported.	None reported.	None reported.	None reported.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Rohm (2008)	Diarrhoea was reported in one propofol patient Postoperative nausea and vomiting were reported in 4 sevoflurane and 6 propofol patients. Shivering was reported in 16 sevoflurane and 10 propofol patients. AnaConDa related adverse events that were reported (no frequency given): hypercapnia, false disconnection from the ventilator, sevoflurane loss during sectioning.	None reported.	1 patient was re-operated on in each study arm. Atrial fibrillation was reported in 10 sevoflurane and 16 propofol patients.	Pericardial tamponade in 1 propofol patient.	Gut ischaemia was reported in 1 propofol patient. Renal insufficiency was reported in 1 patient in each study arm. Respiratory insufficiency was reported in 2 patients in each study arm.	2 patients died in-hospital, 1 in each study arm.
Rohm (2009)	Postoperative nausea and vomiting were reported in 9.4% sevoflurane and 6.6% propofol patients. Agitation was reported in 4.5% sevoflurane and 1.6% propofol patients.	1 patient in each arm experienced renal failure (both after CABG). Both cases resolved without the need for haemodialysis. 1 patient in the propofol arm experienced polyuria.	None reported.	None reported.	Reoperation, respiratory insufficiency and re-intubation were reported not to differ significantly between both arms.	1 patient in the sevoflurane and 2 patients in the propofol group died after long-term ventilation.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Hellstrom (2011)	One AnaConDa patient did not have the device removed prior to extubation, leading to slow awakening due to sedative re-breathing. There was one case of leakage from the sampling line attached to an AnaConDa.	19 propofol arm and 21 sevoflurane arm patients received norepinephrine. 5 propofol arm patients received milrinone or levosimendan.	None reported.	4 propofol arm and 1 sevoflurane arm patients were cardioverted. All cardioversions were carried out after the 12h post-operative period.	1 propofol patient was defibrillated, but had a pre-operatively impaired left ventricular function. 1 sevoflurane patient was defibrillated (they also received an isoprenaline infusion and temporary pacing.	1 sevoflurane patient died within 30 days post-surgery.
Mesnil (2011)	None reported.	None reported.	None reported.	1 patient in the propofol and 3 in the midazolam group required re-intubation.	None reported.	None reported.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Hellstrom (2012)	(See also entry for Hellstrom 2011) 1 propofol and 3 sevoflurane patients had severe pain after extubation. 9 propofol and 12 sevoflurane patients had nausea and vomiting. 1 propofol and 2 sevoflurane patients had shivering.	(See also entry for Hellstrom 2011) 1 sevoflurane patient needed pharmacological treatment for agitation.	(See also entry for Hellstrom 2011) 5 propofol and 3 sevoflurane patients required non-invasive ventilation.	See entry for Hellstrom 2011.	(See also above entry for Hellstrom 2011) There was 1 readmission to ICU in the sevoflurane group and 5 readmissions in the propofol group (p=0.204).	See entry for Hellstrom 2011.
Soro (2012)	None reported.	None reported.	None reported.	None reported.	54.3% patients in the sevoflurane arm and 72.7% patients in the propofol arm required inotropic support .	2 patients died in the sevoflurane arm.
Steurer (2012)	No statistically significant difference in incidence of postoperative nausea and vomiting.	None reported.	No statistically significant difference in pulmonary postoperative complications.	None reported.	None reported.	None reported.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Marcos-Vidal (2014)	Atrial fibrillation incidence in ICU was reported as 27.4% in the propofol arm and 23.9% in the sevoflurane arm (p=0654).	No significant difference in the use of cardiovascular support drugs between study arms was reported.	None reported.	None reported.	None reported.	No deaths reported in the 30-day postoperative period.
Jerath (2015)	None reported.	None reported.	None reported.	None reported.	None reported.	None reported.
Bellgardt (2016)	(See EAC comment for the study)	(See EAC comment for the study)	(See EAC comment for the study)	(See EAC comment for the study)	(See EAC comment for the study)	Hospital mortality in the isoflurane arm was 40% and it was 63% in the IV arms, while 365-day mortality was 50% in the isoflurane arm and 70% in the IV arm. In both cases the differences were statistically significant (p= 005 and p=0.013, respectively).
Jabaudon (2017)	None reported.	None reported.	None reported.	None reported.	Rescue therapy for ARDS was used in 18 sevoflurane and 19 midazolam patients.	1 sevoflurane and 1 midazolam patient died within 2 days of treatment. 9 sevoflurane and 10 midazolam patients died within 30 days of treatment.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Krannich (2017)	Hypercapnia occurred in 7 patients within the isoflurane group.	3 midazolam and 5 isoflurane patients experienced bleeding requiring a blood transfusion.	2 isoflurane patients required percutaneous coronary intervention . 10 midazolam and 16 isoflurane patients reported ventricular tachycardia.	None reported.	Re-arrest occurred in 19 midazolam and 14 isoflurane patients. 4 midazolam and 6 isoflurane patients developed ARDS.	None reported.
Meiser (2018)	None reported.	None reported.	None reported.	None reported.	None reported.	Mortality during continuous lateral rotational therapy was 11% in the isoflurane arm and 21% in the IV arm (p-value was reported as 0.37 in text and 0.39 in Table 3).
Staudacher (2018)	Hypotension and hypercapnia occurred in the isoflurane arm, but it was not specified how often it occurred, but it did not result in termination of the sedation.	Isoflurane sedation was terminated in two patients due to seizures. It was also terminated in one patient due to anisocoria that resolved after a switch to IV sedation.	None reported.	None reported.	None reported.	36.1% of patients in the isoflurane arm and 29.2% of patients in the propofol arm died.

Study	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Foudraine (2021)	None reported.	None reported.	None reported.	None reported.	None reported.	Of those who experienced delirium, 4 IV and 0 sevoflurane patients died in ICU. No whole group mortality figures given.

7 Evidence synthesis and meta-analysis

The EAC did not conduct an evidence synthesis of the reported trials. The company submission states that they intend to carry out a meta-analysis once the SED001 trial has been published. As this is a large trial using sedative agents of particular import with respect to NHS practice (isoflurane and propofol) for which the only other identified study is Staudacher (2018), the EAC believes that it is important that the results of that trial are considered in the meta-analysis.

The EAC notes that one meta-analysis has been published comparing only AnaConDa delivered volatile sedation to IV sedation (Kim 2017). Other meta-analysis mentioned in the company submission includes other devices performing a similar function to the AnaConDa (Landoni 2016, Jerath 2017, Spence 2017). Since the time of the analysis conducted by Kim (2017), the EAC identified further eight published studies that were published regarding the decision problem. The EAC believes seven of these would be included in such a meta-analysis. A high-level overview of the studies included in Kim (2017) and of the studies that have been published since then is presented in table 14 together with how they report on the key outcomes of interest for this assessment. Note, that Sackey 2008 was not included in the company or EAC evidence list (see section 4.2) as it is a follow-up pilot study from a subset of patients from Sackey 2004.

Table 14: Studies of relevance to meta-analysis

Studies included in Kim 2017	
Study	Comment on outcomes
Guerrero Orriach 2013	Did not report on any of the key outcomes of interest and was only included in the analysis of biochemical markers
Hellstrom 2011 & 2012	This study reported on ventilation time (not analysed in this meta-analysis), extubation time, and length of ICU and hospital stay but in this meta-analysis it was only included in the analysis of biochemical markers and incidence of delirium, nausea and vomiting.
Hanafy 2005	This study reported on extubation time, length of ICU stay, length of hospital stay. It also reported on sedation efficiency but this was not considered in this meta-analysis.
Jerath 2015	This study reported on length of ICU and hospital stay. It was also included in the analysis of incidence of nausea and vomiting. The study reported on extubation time, but it was not included in the meta-analysis for this outcome.
Marcos-Vidal 2014	This study reported on length of ICU stay. It was also included in the analysis of biochemical markers. It also reported on length of hospital stay but was not included in the meta-analysis for this outcome, and reported on sedation efficiency which was not included in this meta-analysis.
Mesnil 2011	Extubation time, length of ICU stay. It was also included in the analysis of biochemical markers and delirium incidence. It also reported on ventilation duration and sedation efficiency which were not included in this meta-analysis.
Rohm 2008 & 2009	Extubation time, length of ICU stay, length of hospital stay. It was also included in the analysis of biochemical markers and incidence of delirium, nausea and vomiting. It also reported on ventilation duration and sedation efficiency which were not included in this meta-analysis.
Sackey 2004 & 2008	Extubation time, length of ICU stay (but note that the 2008 publication which reports this only includes data from 17 patients out of 40 included in the 2004 study), the 2008 publication was also included in the analysis of the incidence of delirium. Sackey 2005 reported also on sedation efficiency which was not considered in this meta-analysis.
Soro 2012	This study reported on length of ICU stay, length of hospital stay. It was also included in the analysis of biochemical markers.
Steurer 2012	This study reported on length of ICU stay, length of hospital stay. It was also included in the analysis of biochemical markers.
Studies not included in Kim 2017	
Study	Comment on key outcomes for the assessment report
Bellgardt 2016	Looked at ventilation duration, as well as ICU and hospital length of stay.
Foudraine 2021	Looked at ventilation duration, as well as ICU and hospital length of stay.
Jung 2020	Looked at sedation efficiency, as well as ICU and hospital length of stay.
Krannich 2017	Looked at ventilation duration and ICU length of stay.
Meiser 2018	Looked at ventilation duration, sedation efficiency, as well as ICU and hospital length of stay.
SED001	Looked at extubation time, sedation efficiency and ICU length of stay.
Staudacher 2018	Looked at ventilation duration, sedation efficiency, as well as ICU and hospital length of stay.
Turktan 2019	Did not look at any of the key outcomes, and would not be included in a future meta-analysis.

With regard to the primary outcomes specified by Kim (2017), it was found that the use of AnaConDa delivered sedation was associated with faster wake-up time and faster extubation time, but not in reductions of length of ICU or hospital stay. With respect to the evidence presented in section 5.3 of this report, the EAC believes that it would not change the conclusions of Kim's (2017) meta-analysis. All the studies reporting extubation time or another measure of wake-up time that the EAC identified favoured AnaConDa, so the conclusion for this result would not change. The majority of studies reporting length of ICU or hospital stay found no significant difference between the AnaConDa and the IV arms. Therefore, with respect to the key outcomes, the EAC does not believe that a meta-analysis incorporating any new studies would significantly change the outcome of Kim's meta-analysis. Of note, Kim (2017) did not include data from the Hellstrom studies (2011 & 2012) in its meta-analysis of extubation time and both ICU and hospital LOS, Jerath (2015) data was not included in extubation time meta-analysis, and Marcos-Vidal (2014) length of hospital stay was not included in the meta-analysis.

With regard to the secondary outcomes reported by Kim (2017), the EAC would not include these in the meta-analysis as they were not outcomes identified as of particular importance by the clinical experts (see correspondence log) or as drivers of the economic model. These secondary outcomes were various biochemical markers, and incidence of delirium, as well as postoperative nausea and vomiting. Notably, Kim et al (2017) had high markers of heterogeneity in their analysis ($I^2 > 75\%$) for some of the outcomes, including extubation time. The EAC has discussed in section 5.2 the diversity of the patient population in the included evidence. There are also methodological differences between some studies with respect to secondary outcomes (e.g. Soro 2012 looked at cTnI while other studies looked at cTnT when assessing troponin levels). The EAC believes that the heterogeneity present in these studies is associated with the normal diversity of patients and clinical practice present in ICU practice.

8 Interpretation of the clinical evidence

It is important to reiterate that this report discusses the evidence surrounding the use of the AnaConDa-S device only. While the EAC identified several studies that fit the scope, there is a particular difficulty associated with the fact that AnaConDa-S and the standard of care IV sedation does not utilise the same sedative agents. It is beyond the scope of this report to compare different sedative agents or to state whether either volatile or IV sedation is preferable. Nevertheless, throughout this report studies have often been grouped by the sedative agents used so that clinicians favouring the use of one sedative agent over another can assess the evidence in light of their standard practice. Finally, compared to many other aspects of patient care, there are only general guidelines on the use of sedation within the ICU environment. Patients in ICU are complex and often require highly tailored care, as such the EAC believes that any recommendation made on the basis of this guideline should not restrict the clinician's ability to provide personalised care to the diverse patient population present on the ICU.

As patients in ICU receive multiple concurrent treatments (including polypharmacy and various technological interventions supporting their organ systems), the EAC believes (see correspondence log for expert advice highlighting the presence of confounders) that for the majority of outcomes the type of sedation received will only be one of several factors potentially affecting that outcome. This is particularly relevant for long-term outcomes, for which proving that benefit of anyone particular intervention will be inherently difficult due to the type of care patients receive on ICU. Importantly, even for those outcomes highly dependent on sedation time, such as extubation time and wake-up time, the differences in outcomes are likely attributable to the sedative agents used and not to the presence or absence of the AnaConDa-S device itself.

The company submission and the literature mention one competitor device that performs a similar function to the AnaConDa-S. The EAC did not identify any studies comparing these two devices to each other or any studies that

compared methods of delivery of volatile sedation in the ICU setting. As such, the EAC is unable to comment if the AnaConDa-S offers advantages over other similar technologies that would allow for the provision of volatile sedation in the ICU.

The EAC believe that these points place a limit on the conclusions that can be derived from the available evidence with respect to the benefit of the AnaConDa-S device itself. AnaConDa-S allows clinicians to deliver a sedation strategy that is associated with faster extubation and wake-up times. Based on the available studies, the EAC cannot comment whether this sedation strategy is of particular benefit to any subgroup population but acknowledges the experts' statement that it might be particularly useful in patients suffering from bronchospasm (see correspondence log). As such, the EAC believes that availability of a device that permits clinicians to use this sedation strategy is of benefit to patients.

8.1 *Integration into the NHS*

Discussions with the clinical experts (see correspondence log) highlight that AnaConDa-S is already being used within the NHS. Some experts use it for sedating a variety of ICU patients while other clinicians only use it only in patients with bronchospasm. AnaConDa-S can be easily used within the sedation framework outlined by Grounds (2014) as it allows for a variety of sedatives to be used and does not pre-specify the devices via which these sedatives should be delivered. As such, the EAC does not believe that there are any obstacles that would be prohibitive in the wider adoption of AnaConDa-S. Nevertheless, while common, the use of volatile sedatives in the ICU is an off-label use of these pharmacological agents (see correspondence log).

Guidelines for the Provision of Intensive Care Services (2019) state that in point 1.5.4 that 'all staff must be appropriately trained in and competent and familiar with the use of equipment'. The company states (see correspondence log) that it does provide such training free of charge. Regarding which staff are trained in setting-up the AnaConDa-S on a patient, practice varies

between centres (see correspondence log) and includes a mix of nursing and scientific/technical staff. Importantly, the challenges of using specialist equipment are common in the ICU and while the adoption of the AnaConDa-S would provide another technology in which ICU staff would need to be trained, ICUs are well versed in managing their technological requirements, often having dedicated staff to ensuring that competence is maintained in the use of these devices (Guidelines for the Provision of Intensive Care Services 2019). Similarly, human factors relating to the use of AnaConDa are likely to be the same as those concerning other ICU equipment.

Environmental Exposure Considerations

UK Health and Safety regulations (EH40/2005) specify the concentration of certain compounds to which workers can be exposed. These regulations specify that for isoflurane the long-term exposure should not exceed 50 parts per million (ppm) and time weight average of 383 mg/m^3, while for sevoflurane there is no prespecified safety limit. Environmental exposure with the volatile sedative delivered via AnaConDa was studied using various scavenging system. Pickworth (2013) used the Deltasorb system with both volatile agents, Bos (2017[only available as a poster presentation]) used FlurAbsorb with sevoflurane, while both Sackey (2005) and Herzog-Niescery (2018) used active scavenging in combination with isoflurane. Sackey (2005) also looked at environmental concentrations when scavenging was disconnected while Herzog-Niescery (2018) looked at isoflurane spillage situations. In all these studies concentrations were consistently reported as below 2ppm except in care situations, where the ventilatory circuit might be opened, where the levels would not exceed 10ppm. As such, the use of AnaConDa with a scavenging system is likely to comply with UK staff exposure regulations.

There is a lack of comparative evidence on the consumption of volatile sedatives in the ICU setting when these are delivered via AnaConDa-S compared to other methods of volatile sedative delivery. Sackey (2005) compared isoflurane consumption in their study to that of Spencer (1992), noting that under an assumption of a minute ventilation volume of 7.5 litres and an inspired concentration of isoflurane of 0.3% the AnaConDa would be

associated with 75% reduction of the agent used. The EAC though notes that the technology utilised in Spencer (1992) might not reflect present day comparators (whether similar technologies to AnaConDa or anaesthetic machines). Similarly, technological advances in mechanical ventilator technologies, both since the Spencer and Sackey studies, might also impact these estimates. The EAC notes that the ventilator used in the Spencer study was in use before 1980 (Rawlings 1980), while Slinger (1990) notes that the user manual for the vaporiser used in the Spencer study was issued in 1985. As such, there is uncertainty about whether the use of the AnaConDa would be associated with a lower consumption of volatile sedatives compared to other state-of-the-art means of delivering volatile sedation.

8.2 *Ongoing studies*

The EAC searched the ClinicalTrials.gov and EU-CTR registries for relevant ongoing trials (see Appendix A for details). The identified studies are listed below (Table 15). Briefly, the EAC identified six ongoing trials, including the SED001 trial for which several registered sub-studies were identified. Only one study is focusing on the paediatric population. Additionally to the studies summarised in table 15, 2010-020044-35 and 2007-002925-64 mention AnaConDa, but trial information is only available in French.

Table 15: Potentially relevant ongoing studies

Trial ID	Title	Recruitment Status	Target size	Intervention	Condition	Primary outcome
EudraCT 2016-004551-67 (SED001) Encompassing the following sub-studies: DRKS00018958 DRKS00020364 DRKS00020237 DRKS00020240 DRKS00018959	A randomised, controlled, open-label study to confirm the efficacy and safety of sedation with isoflurane in invasively ventilated ICU patients using the AnaConDa administration system	Complete	301 (actual enrolment)	AnaConDa (isoflurane) vs IV propofol	ICU patients	Percentage of time on adequate sedation depth.
NCT01983800	AnaConDa long term sedation study (VALTS)	Complete	60 (actual enrolment)	AnaConDa (isoflurane) vs IV propofol / midazolam	ICU patients	Atmospheric volatile concentration; Sedation; Feasibility; Education tool; Serum fluoride levels
EudraCT 2019-004537-16	Comparison of an inhaled sedation strategy to an intravenous sedation strategy in ICU patients treated with invasive mechanical ventilation	Ongoing	250	AnaConDa (isoflurane) vs IV propofol / sufentanil	Patients mechanically ventilated for at least 24h	Incidence of delirium
NCT04684238	Effect & safety of inhaled isoflurane vs iv midazolam for sedation in mechanically ventilated children 3-17 years old	Ongoing	160	AnaConDa (isoflurane) vs IV midazolam	Paediatric patients mechanically ventilated for at least 12h	Percentage of time adequate sedation depth
EudraCT 2007-006087-30	Efficiency and safety of inhalative sedation with sevoflurane in comparison to an intravenous sedation concept with propofol in intensive care patients: study protocol for a randomized controlled trial	Ongoing	100	AnaConDa (sevoflurane) vs IV propofol / midazolam	Patients mechanically ventilated for at least 24h	Time to extubation or persistent spontaneous breathing after stopping sedation
NCT01802255	Sevoflurane- safety in long-term sedation procedures	Unknown	50	AnaConDa (sevoflurane) vs IV midazolam	Patients sedated for at least 48h	Maintenance of renal function

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted a broad search rather than focusing on the key concepts of the scope. In particular, the intervention criteria used were concerned with specific anaesthetic rather than the AnaConDa-S device. The search was conducted across four databases on the 17th July 2020, identifying in total 571 references. The search strategies were comprehensive using a combination of free text terms, indexed terms and economic terms. However, the search strategies failed to include the term 'anaconda'. The company identified two records that were considered relevant for inclusion (Sackey 2018, L'Her 2008).

To ensure that all relevant and recent literature had been identified, the EAC conducted their own combined systematic searches for both clinical and economic evidence, no additional evidence was identified for inclusion. Details of the company and EAC searches are provided in appendix A.

Published economic evidence review

The company submission included two studies (L'Her 2008 & Sackey 2018) that reported some economic outcomes. The EAC searches identified the same two studies and no additional published evidence.

While the EAC agreed that both studies provide some relevant evidence for the cost of inhaled sedation using AnaConDa-S compared with IV sedation, the evidence provided by these studies is extremely limited. One is a conference abstract (Sackey 2018) reporting briefly on a decision analytic model comparing inhaled sedation using AnaConDa-S with IV sedation using either propofol or midazolam. The second study (L'Her 2008) is an observational study assessing costs of isoflurane using AnaConDa-S including very limited cost comparisons which are reported in Euros.

The EAC has therefore not included a detailed data extraction and appraisal of these studies. A brief description of the methods (table 16) and findings

(table 17) are reported here for information with additional details reported in the company economic submission (sections 1 and 2).

Table 16: Economic Study Summaries

Study	Setting and Participant Information	Outcomes	EAC Comment
L'Her 2008 **Location** France **Design** Prospective observational study assessing feasibility, benefits and costs of routine isoflurane sedation via AnaConDa	ICU • 15 patients requiring >24 hours deep sedation • ventilated patients were switched from standard of care (IV midazolam) to inhaled isoflurane with AnaConDa	• Feasibility and Efficacy of isoflurane sedation with AnaConDa	• No de novo cost modelling • No detailed resource reporting •
Sackey 2018 **Location** Germany **Design** Decision Analytic model (comparative)	ICU • 200 long term ventilated patients • IV ventilation with either propofol or midazolam	• Incremental cost of inhaled sedation with Anaconda versus propofol/midazolam • Deaths avoided	• Abstract Only • Clinical data taken from Bellgardt 2016 • No reporting of cost or resource parameter sources • Utilities and thresholds referred to but no details around these to verify source or use. • No model details available therefore model structure, approach and inputs cannot be verified

Results from the economic evidence

Results from two studies (Sackey 2018, L'Her 2008) reported cost savings with inhaled isoflurane via AnaConDa-S compared with IV propofol or midazolam (Table 17). Clinical, cost and resource data reporting for both studies are limited and cannot be validated therefore results presented here are for information only. One study (Sackey 2018) reported a 41% reduction in in-patient deaths with an associated cost saving of £15,042 per patient leaving hospital alive. The study author, who is a company employee, provided information that this result was based on Kaplan-Meier and log rank comparison of hospital mortality and 365-day mortality reported in Bellgardt

2016. Adjusted odds ratios (ORs) [with 95% confidence interval (95% CI)] were calculated by logistic regression analyses to determine the risk of death after isoflurane sedation. These ORs were then used to estimate the UK modelled scenario. The author notes that there is currently no full publication, only a conference abstract. When asked, five clinical experts indicated that deaths avoided was a very poor outcome measure. Reasons for this included; cause of death on ICU is heterogenous, attributed cause of death to sedation regimen would be very difficult and there is no data to suggest a reduction in deaths with inhaled sedation. For this reason, the EAC consider cost savings associated with reduced deaths to be of extremely limited value at this time.

Table 17: Results from published cost analyses

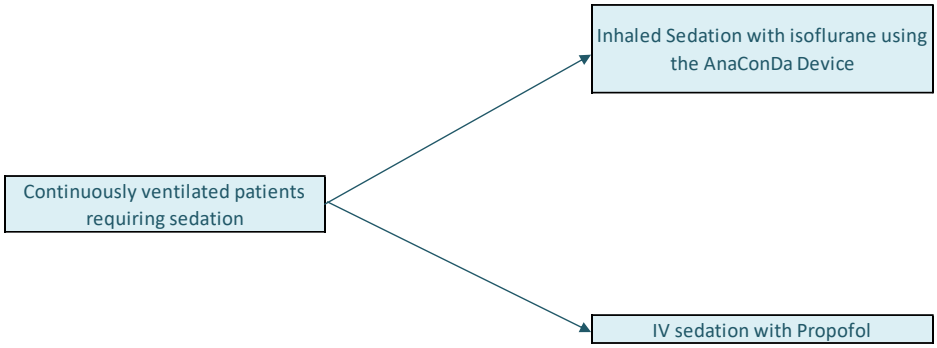
Study	Results
L'Her 2008	• Overall daily cost of sedation protocols (Inhaled with AnaConDa versus IV sedation) did not differ • Mean (SD) cost of IV sedation was €171 (±€101) compared with €122 (±€44) for inhaled sedation with AnaConDa • 7 of 15 patients had an above average midazolam requirement with associated increased costs but in this subset of patients, inhaled isoflurane with AnaConDa allowed achievement of sedation goal in all cases resulting in a significant cost difference (€218 (±111) vs €110 (±19), P < .01.
Sackey 2018	• Estimated incremental cost of inhaled isoflurane via AnaConDa versus propofol/midazolam was £3,861 per patient • Estimated 41% reduction in in-patient deaths with a cost per additional patient leaving hospital alive of £15,042. • Estimated 30% reduction in 365-day deaths with a cost per death avoided at 365 days of £18,285 • Results estimated that if patients surviving for 365 days survive for a further six months at a threshold utility of 0.61, the use of AnaConDa would be considered cost-effective at a threshold of £20,000 per QALY

9.2 *Company de novo cost analysis*

Economic model structure

The company submitted a cost consequence analysis using a simple decision tree structure comparing inhaled sedation using the AnaConDa-S device and IV sedation (Figure 3). The model has a 30-day time horizon and included patients requiring mechanical ventilation for ≥24 hours in ICU. The model is based on an NHS and personal social services perspective. No discounting is applied, which is appropriate for the time horizon.

Figure 3: Model Structure for Inhaled sedation using AnaConDa-S versus IV sedation



Comparisons in the model

The company base-case compares inhaled isoflurane with AnaConDa-S to IV propofol using unpublished data from the SED001 trial assuming [redacted]. In the base-case analysis, data are taken from a subset of patients (non-switchers) in the SED001 trial. These patients were the patients who remained on the assigned approach to sedation (inhaled or IV) for the duration of the trial follow-up.

Additional scenario analyses were also submitted:

- inhaled isoflurane with AnaConDa-S vs IV propofol: SED001 data, reduced days in ventilation for patients sedated using isoflurane with AnaConDa
- inhaled isoflurane with AnaConDa-S vs IV propofol: SED001 data, reduced days ventilation and reduced days in ICU for the whole trial population including switchers.
- inhaled isoflurane with AnaConDa-S vs IV midazolam: using published data from Krannich 2017

The EAC has also included an additional comparison for inhaled sevoflurane with AnaConDa-S compared to IV propofol as clinical expert input suggests that sevoflurane is used in the UK although less commonly than isoflurane.

Assumptions in the Model

The company included a small number of assumptions in the submitted base-case model. Table 18 summarises the assumptions included by the company and additional assumptions identified by the EAC.

Table 18: Assumptions in Model

Assumption	Justification	EAC comment
Isoflurane is the drug used for inhaled sedation	• Clinical expert input to the company indicates this is the most commonly used drug	The EAC notes that clinical expert opinion supports this assumption. Sevoflurane is used but is less common. The EAC will explore this in a scenario analysis.
Propofol is the most common drug used for IV sedation	• Clinical expert input to the company indicates this is the most commonly used drug	The EAC notes that clinical expert opinion supports this assumption. Midazolam is used for sedation of children and this will be explored in a scenario analysis and notes that the company has included a scenario analysis comparing with Midazolam but in adults.
Sedation efficacy, tolerability and safety do not differ by sedation strategy (Inhaled isoflurane using AnaConDa versus IV sedation)	• SED001 (unpublished) reported no difference between isoflurane via AnaConDa compared with IV propofol • Evidence evaluated during the clinical literature review supports this conclusion of the SED001 trial	The EAC agrees with the assumption that there is no different in these measures by sedation strategy.
There are differences in sedation costs, monitoring and administration by sedation strategy	• Small differences in drug costs • Key differences for device, equipment and consumables	The EAC agrees with this assumption
IV sedation requires more frequent dose renewal	• When using IV sedatives the syringes with the drugs need to be changed more often due to a higher consumption rate of the agent	The EAC agrees with this assumption

Daily sedation interruption protocols are more likely with IV sedation	• To avoid sedative accumulation and over-sedation when using IV sedation.	The EAC agrees with this assumption
Additional assumptions identified by the EAC		
Mean Adult weight is 70kg	The company submission included an assumption that mean adult weight in the UK is 70kg and this was used to calculate the required dose and cost of drugs. No source was provided for this value. The EAC has used the mean body weight from SED001.	
Inclusion of a mixed gas analyser as a cost associated with AnaConDa	Not all units will require a gas analyser as some may already have suitable analysers. The EAC has not removed this cost noting it is potentially a conservative assumption.	
Days of Gas Analyser use is based on 180 days use per year with replacement every five years	Gas Analyser costed in the model and the assumption for number days of use have been provided by the company. No source for the estimated number of days has been provided however the EAC note that the cost of the gas analyser is a small cost in the model and will not impact cost savings.	
Training to move from IV sedation to inhaled sedation using AnaConDa will be required	The company submission does not include any costs for training staff to deliver inhaled sedation using AnaConDa. The EAC has included a cost for training in the model, however it is a conservative cost.	
Additional Assumptions Made by EAC		
Specific training costs are incurred primarily at the outset of moving to inhaled sedation with AnaConDa and will involve all key ICU staff	Once staff on a unit have been trained in inhaled sedation delivery, it is assumed that ongoing training and training of new staff will largely be part of normal staff training processes.	
For certain training elements there is a cost associated with the staff time	AnaConDa specific training is provided free of charge by the company	
Per patient cost of training assumes that 100 patients would be sedated using inhaled sedation with AnaConDa	The EAC note that per patient training costs to deliver inhaled sedation using AnaConDa to reduce the more patients are sedated using AnaConDa.	

Economic model parameters

The company submission included a short list of clinical and cost parameters.

These are detailed in the following sections.

Clinical parameters and variables

The key clinical parameters (table 19) in the company submission include the mean number of days on a ventilator and the mean total number of days in ICU. Data for the company base-case for both these outcomes has been taken from a subset of patients in the SED001trial.

Table 19: Clinical parameters used in the company's model and any changes made by the EAC

Parameter	Company submission	Source	EAC value	Source	Comment
Mean weight of adult patient in ICU	70kg	Source not provided by the company	[redacted]	SED001	Mean weight in SED001 was [redacted] for the whole population. No indication that this was different for the 'non-switchers' subset.
BASE CASE: Inhaled isoflurane using AnaConda versus IV Propofol					
Inhaled isoflurane using AnaConDa					
Mean duration of ICU stay (days)	[redacted]	SED001 (unpublished)	No Change	SED001	These values are taken from the company trial data. The EAC has not identified any alternative source for this parameter but will explore the impact of changes to these values in a sensitivity analysis. The reported outcome appears to be ICU free days in a 30-day period and the value in the model for Mean duration of ICU stay appears to have been calculated by subtracting the ICU free days value from 30. The data are calculated using only the population of patients who do not switch sedation protocols [redacted] and not the full trial population [redacted]
Number of days on Ventilator	[redacted]	SED001 (unpublished)	No Change	SED001	This is a mean value applied to both intervention and comparator. The company submission does not provide details of how this was calculated but it appears to be the mean of the number of ventilator days for isoflurane and propofol reported in SED001.

Parameter	Company submission	Source	EAC value	Source	Comment
					Clarification from the company confirmed that ventilation days set to mean for whole cohort (both arms) based on non-significant difference [redacted] The data are calculated using only the population of patients who do not switch sedation protocols [redacted] and not the full trial population [redacted].
IV Propofol					
Duration of ICU stay (days)	[redacted]	SED001 (unpublished)	No Change	SED001	These values are taken from the company trial data. The EAC has not identified any alternative source for this parameter but will explore the impact of changes to these values in a sensitivity analysis. The reported outcome appears to be ICU free days in a 30-day period and the value in the model for Mean duration of ICU stay appears to have been calculated by subtracting the ICU free days value from 30. The data are calculated using only the population of patients who do not switch sedation protocols [redacted] and not the full trial population [redacted].
Number of days on Ventilator	[redacted]	SED001 (unpublished)	No Change	SED001	This is a mean value applied to both intervention and comparator. The company submission does not provide details of how this was calculated but it appears to be the mean of the number of ventilator days for isoflurane and propofol reported in SED001.

Parameter	Company submission	Source	EAC value	Source	Comment
					Clarification from the company confirmed that ventilation days set to mean for whole cohort (both arms) based on non-significant difference [redacted] The data are calculated using only the population of patients who do not switch sedation protocols [redacted] and not the full trial population [redacted]
Training Time	Not included	Not included	6 hours	Company	Based on the training elements and courses provided by the company which are considered to be outside of normal staff time and training (see Appendix D for details)
Staff involved in training	Not included	Not included	17	Guidelines for the Provision of Intensive Care Services (2019)	Based on the assumption that a critical care unit with a 9-16 bed capacity is recommended to have 2 consultants, 1 nurse educator, 12 registered nurses and 2 senior registered nurses.
SCENARIO ANALYSIS for INHALED ISOFLURANE with ANACONDA versus IV PROPOFOL					
Isoflurane: Mean number of days on Ventilator	[redacted]	SED001 (unpublished)	No Change	SED001 (unpublished)	The company submission included a scenario analysis which used the mean number of days on a ventilator for each arm as reported in the SED001 trial to reflect a difference in the number of ventilation days.
Propofol : Mean number of days on Ventilator	[redacted]	SED001 (unpublished)	No Change	SED001 (unpublished)	The company submission included a scenario analysis which used the mean number of days on a ventilator for each arm as reported in the SED001 trial to reflect a difference in the number of ventilation days

Resource identification, measurement and valuation

The key resource inputs in the company submission for inhaled sedation with AnaConDa-S are the costs of the AnaConDa-S device and necessary accessories such as filters and multi-gas analyzers (table 20). The EAC note that not all centres would need to purchase a gas analyser as they may already has access to one so this is a conservative approach to AnaConDa-S costs.

Resource costs for IV sedation include costs for infusion syringes and nurse time required for syringe changes. An additional cost for daily sedation interruption (DSI) is also included.

No training costs have been included in the company submission. Correspondence with the company (see correspondence log) indicated that the company provide several training options free of charge to units wanting to introduce inhaled sedation using the AnaConDa-S device. Although the training is free of charge there is a staff time involvement for ICU staff to take part in the training. A nominal cost of training has therefore been included in the EAC model based on assumptions and costs briefly outlined in table 20 (full details in appendix D). While quite high at £621.60 per patient, the costs for training that have been included in the model are conservative. It is unlikely that staff in ICU would have to undergo regular training outside of that which forms part of their normal competency training. In addition, if more patients are sedated using inhaled sedation with AnaConDa-S, the cost per patient for training would be lower.

Table 20: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	Source	EAC value	Source	Comment
IV Sedation with Propofol Costs					
Drug Costs					
Propofol Unit Costs	£2.08	eMIT: Pharmex data for the period 01/01/19 - 31/12/19, for Pharmex products shown as Generic in the period 01/07/19 - 31/12/19	£5.00	BNF	The EAC has used BNF costs for consistency. Cost of a 50ml vial (10mg/ml propofol) Three prices available • £5.00 for a single 50ml vial, • £10.45 per vial based on a pack of 10 at £104.49 • £12.06 per vial based on a pack of 10 at £120.60 The EAC has used the lower cost in the model but explored the impact of the higher cost in a sensitivity analysis.
Propofol Dose per patient	210mg/hour	Dose based on recommended dose of 3mg/per/kg	180.6mg/hour	BNF	Based on a median dose of 2.15mg/kg/hour (BNF recommended dose 0.3-4mg/kg/hour)
Number of vials per hour	0.42	Based on a need for 210mg per hour to achieve 3mg/kg/hour for a 70kg adult	0.36	Based on a need for 185mg per hour to achieve 2.15mg/kg/hour (based on a median value of BNF dosing recommendations) for an [redacted] adult (as reported in SED001)	The EAC has used the same calculation but with different dose and weight values.

Parameter	Company value	Source	EAC value	Source	Comment
Propofol cost per hour	£0.87	Unit cost per vial divided by number of vials needed per hour (£2.08/0.42)	£1.81	Unit cost per vial divided by number of vials needed per hour (£5.00*0.36)	
Duration of sedation with Propofol	[redacted]	Mean duration of propofol sedation required in SED001 based on a mean value for both propofol and isoflurane	No Change	SED001	Based on a mean [redacted] days of sedation with propofol and [redacted] days with isoflurane as reported in SED001.
Total Cost of Propofol per patient	**£228.53**	**Drug acquisition cost based on £0.87 per hour for [redacted] hours**	**£472.45**	**Drug acquisition cost based on £1.81 per hour for [redacted] hours**	**The EAC total cost for propofol is higher than the company costs as it is based on a higher propofol unit cost. The company costs are conservative and EAC changes increase the cost saving.**
Additional Costs for IV Sedation					
Additional Sedation Cost per day	£327.87 (£30.08 per day for [redacted] days, comprising £20 per hour nurse time and £1 per syringe with 10 syringes required)	Unclear Company submission states it is a nominal unit cost of supply and disposal of infusion syringes and allocates a cost of nurse time for does renewal and syringe change	£639.50	PSSRU 2020 Cost of band 6 hospital-based nurse: £50 per hour. No change to the cost of syringes but the changes to the propofol dose result in only 9 syringes being needed. Total cost per day of £58.67 for [redacted] days.	Clarification from the company indicated that the cost of nurse time was taken from PSSRU but did not include overheads. The EAC has used the cost of a band 6 hospital-based nurse including overheads.

Parameter	Company value	Source	EAC value	Source	Comment
Daily Sedation Interruption	£218 (£20 per day for [redacted] days)	Unclear Based on assumption that daily sedation interruption is a 30 minutes procedure and involves 2 nurses costed at £20 per hour.	£545	PSSRU 2020 Cost of band 6 hospital-based nurse: £50 per hour 2 nurses for 30mins per day for [redacted] days	Clarification from the company indicated that the cost of nurse time was taken from PSSRU but did not include overheads. The EAC has used the cost of a band 6 hospital-based nurse including overheads.
TOTAL COST OF IV SEDATION WITH PROPOFOL	**£774.41**		**£1656.94**		
Inhaled sedation with Isoflurane Costs					
Drug Costs					
Isoflurane Unit Cost	£35.29	BNF Based on the cost of a 250ml bottle	£35.29	BNF	
Isoflurane dose per patient	3ml per hour	SED001 Study	3ml per hour	SED001 study	The EAC has not changed this value as it is the reported does in the study from which to rest of the clinical data is taken for consistency. The EAC noted that clinical expert input suggested that the typical rate would be 8-10ml per hour and has explored the impact of the higher dose in a sensitivity analysis.
Isoflurane cost per hour	£0.42	Drug acquisition cost divided by total hours sedation.	£0.42	No change	

Parameter	Company value	Source	EAC value	Source	Comment
Duration of sedation with isoflurane	[redacted]	Mean duration of propofol sedation required in SED001 based on a mean value for both propofol and isoflurane	[redacted]	SED001	Based on a mean [redacted] days of sedation with isoflurane and [redacted] days with propofol as reported in SED001.
Total cost of isoflurane per patient	**£110.78**		**£110.78**		
AnaConDa Device Costs					
AnaConDa Device	[redacted]	Company price list	No Change	Company price list	1 device per day ([redacted]) for [redacted], rounded up to [redacted]
Syringes (50ml)	[redacted]	Company price list	No Change	Company price list	1.44 syringes ([redacted]) needed per day for [redacted] rounded up to [redacted]
FlurAbsorb	[redacted]	Company price list	No Change	Company price list	Mean 4 days use per filter **********
New fill adapter	[redacted]	Company price list	No Change	Company price list	Mean 4 days use per adapter [redacted]
Measure line	[redacted]	Company price list	No Change	Company price list	Mean 4 days use per line [redacted]
Nafion tubing	[redacted]	Company price list	No Change	Company price list	Mean 4 days use [redacted]
Multigas analyzer	[redacted]	Company price list	No Change	Company price list	Mean 900 days use per analyser [redacted]
Accessories Kit	[redacted]	Company price list	No Change	Company price list	1 kit per patient
Total Device Costs	[redacted]	**Company Submission**	[redacted]	**Company price list**	
Total Training Costs	**£0**		**£621.60**	Based on the training required and staff time	Although the company provides training to staff free of charge, the EAC consider that for some

Parameter	Company value	Source	EAC value	Source	Comment
				involvement. See appendix D for full details.	elements of training there is a staff time cost implication.
Propofol ICU bed day with ventilation	£1,218 per day	NHS Reference Costs. Main Schedule. 2018/19. National average unit cost for critical care	£1463.41 per day	NHS Reference Costs 2018/19 for adult critical care in standard locations	Weighted mean of all codes except '0 organs supported'
Propofol ICU bed day with no ventilation	£933 per day	NHS Reference Costs	£914.82 per day	NHS Reference Costs 2018/19 for adult critical care in standard locations	Weighted mean of all codes for'0 organs supported'
Isoflurane ICU bed day with ventilation	£1,218 per day	NHS Reference Costs	£1463.41 per day	NHS Reference Costs 2018/19 for adult critical care in standard locations	Weighted mean of all codes for '0 organs supported'
Isoflurane ICU bed day with no ventilation -	£933 per day	NHS Reference Costs	£914.82 per day	NHS Reference Costs 2018/19 for adult critical care in standard locations	Weighted mean of all codes except '0 organs supported'
TOTAL COST OF INHALED SEDATION WITH ISOFLURANE	**£15,999.43**		**£19,263.27**		
TOTAL COST OF IV SEDATION WITH PROPOFOL	**£19,648.61**		**£23,097.03**		

Sensitivity analysis

The company submission included a one-way sensitivity analysis in which the values for key parameters in the model were varied by ±20% of the base-case values. The company submission also included a threshold analysis to investigate the impact of varying the duration of mechanical ventilation in the model.

The EAC conducted similar one-way sensitivity analysis by varying the individual parameters by ±20% as well as a two-way threshold analysis to investigate the impact of changing key parameters in the model.

The results of the sensitivity analysis are discussed in section 9.3.

9.3 *Results from the economic modelling*

Base case results

The company base-case indicates a cost saving of £3,649 per patient for inhaled sedation with isoflurane using the AnaConDa-S device compared with IV sedation with Propofol (table 21).

The EAC made some minor changes to the model. These included changes to the dose and cost of propofol, changes to cost of nurse time and the addition of training costs for moving to inhaled sedation with AnaConDa-S from IV sedation. Despite the addition of a cost of training of £621.60 per patient to the cost of inhaled sedation using AnaConDa-S, the changes made by the EAC result in an increase in potential cost savings to £3,833.76.

Overall, drug acquisition costs were higher for propofol in the EAC model due to the higher dose of propofol required. The total cost of ICU was higher for IV sedation than for inhaled sedation due to a longer stay. Therefore, despite the additional device cost, consumable costs and the potential training costs, inhaled sedation delivered using the AnaConDa-S device remains cost saving compared with IV sedation. The values used by the company and the EAC in the model are taken from a subset of trial patients (non-switchers) so the certainty of a reduction in ICU bed days with inhaled sedation should be considered carefully.

Table 21: Summary of base case results

Model	Cost of Intervention (Inhaled isoflurane using AnaConDa-S)	Cost of Comparator (IV Propofol)	Cost Saving
Company Base-case	£15,999.43	£19,647.73	£3,648.31
EAC Preferred Values	£19,263.27	£23,097.03	£3,833.76

Scenario Analyses

Scenario 1: Days on ventilation are different for the sedation methods

A scenario analysis included by the company indicated that if the mean duration of ventilation for each individual arm reported in SED001 was used in the model ([redacted] and [redacted] the cost saving associated with inhaled sedation using AnaConDa increased to £4,497 per patient (table 22) due to a reduction in cost of ICU ventilated bed days for inhaled sedation with AnaConDa-S.

Using the EAC preferred values for all other inputs, the cost saving when varying the mean duration of ventilation was £5,395.98.

Scenario 2: ICU length of stay for total study population

In the second scenario analysis the duration of mechanical ventilation and duration of ICU stay for the whole study population included switchers. This resulted in a reduced cost-saving for inhaled isoflurane using AnaConDa-S compared with IV propofol of £1,034.66 per patient (table 22).

Using the EAC preferred values for all other inputs, the cost saving when using the mean duration of ICU stay and mean duration of ventilation for the total trial population including switchers was £1,574.30.

Scenario 3: Sevoflurane for inhaled sedation

Clinical expert input indicated that sevoflurane is also used for inhaled sedation in the NHS. The cost of sevoflurane is £123 per 250ml (BNF) and one clinical expert indicated that the dose range would be 5-15ml per hour.

Using a median value of 10ml per hour, the impact of using sevoflurane instead of isoflurane reduced the cost savings to £2,657.08.

Table 22: Summary of Scenario Analysis for Isoflurane and Propofol

Model	Cost of Intervention (Inhaled isoflurane using AnaConDa-S)	Cost of Comparator (IV Propofol)	Cost saving
Scenario 1: Days on ventilation are different for the sedation methods			
Company Scenario 1 (difference in ventilator days and ICU days between IV and inhaled sedation)	£15,507	£20,004	£4,497
Using EAC Preferred Values	£18,401.65	£23,797.63	£5,395.98
Scenario 2: ICU length of stay for total study population			
Company Scenario 2 (difference in ventilator days and ICU day in population including switchers)	£20,107.00	£21,141.66	£1,034.66
Using EAC Preferred Values	£23,725.85	£25,300.15	£1,574.30
Scenario 3: Sevoflurane for inhaled sedation			
EAC Additional Scenario: Sevoflurane for inhaled sedation with AnaConDa	£20,439.95	£23,097.03	£2,657.08

Sensitivity analysis results

In the company submission, inhaled isoflurane via AnaConDa-S remained cost saving in all cases. The key driver for cost savings is the mean duration of mechanical ventilation. Results from the EAC sensitivity analysis, based on EAC preferred inputs, concurred with this assessment (Figure 4). This is because the longer a patient requires sedation and subsequent ICU stay the greater the costs incurred, primarily as a result of the cost of ICU bed days.

Figure 4: Tornado Diagram

The company threshold analysis indicated that if the duration of mechanical ventilation is the same for both methods of sedation, the duration of non-ventilated ICU days needs to be 0.33 days lower for isoflurane via AnaConDa-S for there to be zero cost impact. EAC threshold analysis (again based on EAC preferred values) indicated that if the duration of mechanical ventilation was the same for both sedation methods, the duration of non-ventilated ICU days would need to be in the region of 0.2 days lower for inhaled sedation using AnaConDa-S compared to IV propofol, to remain cost saving (Figure 5).

Figure 5: Two-way sensitivity analysis comparing duration of ICU stay when duration of mechanical ventilation remains the same in both arms

		Duration of Additional ICU Stay AnaConDa													
	-£3,833.76	18	17	16.5	16.3	15.5	15	14.5	14.2	13.5	13	12.5	12.4	11.5	10.5
Propofol	18	£8.49	-£906.33	-£1,363.74	-£1,546.71	-£2,278.56	-£2,735.97	-£3,193.38	-£3,467.83	-£4,108.20	-£4,565.61	-£5,023.02	-£5,114.50	-£5,937.84	-£6,852.66
	17	£923.31	£8.49	-£448.92	-£631.89	-£1,363.74	-£1,821.15	-£2,278.56	-£2,553.01	-£3,193.38	-£3,650.79	-£4,108.20	-£4,199.68	-£5,023.02	-£5,937.84
	16.5	£1,380.72	£465.90	£8.49	-£174.48	-£906.33	-£1,363.74	-£1,821.15	-£2,095.60	-£2,735.97	-£3,193.38	-£3,650.79	-£3,742.27	-£4,565.61	-£5,480.43
	16.3	£1,563.68	£648.86	£191.45	£8.49	-£723.37	-£1,180.78	-£1,638.19	-£1,912.63	-£2,553.01	-£3,010.42	-£3,467.83	-£3,559.31	-£4,382.65	-£5,297.47
	15.5	£2,295.54	£1,380.72	£923.31	£740.34	£8.49	-£448.92	-£906.33	-£1,180.78	-£1,821.15	-£2,278.56	-£2,735.97	-£2,827.45	-£3,650.79	-£4,565.61
	15	£2,752.95	£1,838.13	£1,380.72	£1,197.75	£465.90	£8.49	-£448.92	-£723.37	-£1,363.74	-£1,821.15	-£2,278.56	-£2,370.04	-£3,193.38	-£4,108.20
	14.5	£3,210.36	£2,295.54	£1,838.13	£1,655.16	£923.31	£465.90	£8.49	-£265.96	-£906.33	-£1,363.74	-£1,821.15	-£1,912.63	-£2,735.97	-£3,650.79
	14.2	£3,484.80	£2,569.98	£2,112.57	£1,929.61	£1,197.75	£740.34	£282.93	£8.49	-£631.89	-£1,089.30	-£1,546.71	-£1,638.19	-£2,461.53	-£3,376.35
	13.5	£4,125.18	£3,210.36	£2,752.95	£2,569.98	£1,838.13	£1,380.72	£923.31	£648.86	£8.49	-£448.92	-£906.33	-£997.81	-£1,821.15	-£2,735.97
	13	£4,582.59	£3,667.77	£3,210.36	£3,027.39	£2,295.54	£1,838.13	£1,380.72	£1,106.27	£465.90	£8.49	-£448.92	-£540.40	-£1,363.74	-£2,278.56
	12.5	£5,040.00	£4,125.18	£3,667.77	£3,484.80	£2,752.95	£2,295.54	£1,838.13	£1,563.68	£923.31	£465.90	£8.49	-£82.99	-£906.33	-£1,821.15
	12.4	£5,131.48	£4,216.66	£3,759.25	£3,576.29	£2,844.43	£2,387.02	£1,929.61	£1,655.16	£1,014.79	£557.38	£99.97	£8.49	-£814.85	-£1,729.67
	11.5	£5,954.82	£5,040.00	£4,582.59	£4,399.62	£3,667.77	£3,210.36	£2,752.95	£2,478.50	£1,838.13	£1,380.72	£923.31	£831.83	£8.49	-£906.33
	10.5	£6,869.64	£5,954.82	£5,497.41	£5,314.44	£4,582.59	£4,125.18	£3,667.77	£3,393.32	£2,752.95	£2,295.54	£1,838.13	£1,746.65	£923.31	£8.49
		£16,475.25	£15,560.43	£15,103.02	£14,920.05	£14,188.20	£13,730.79	£13,273.38	£12,998.93	£12,358.56	£11,901.15	£11,443.74	£11,352.26	£10,528.92	£9,614.10

The unit cost of propofol potentially varies widely; the company unit cost of propofol was £2.08 whereas the EAC unit cost was £5.00. Costs reported on BNF varied from £5.00 to £12.06 per vial. In addition to varying propofol costs ±20%, the EAC investigated the impact of using a mean cost of propofol (£9.16) based on all costs reported in the British National Formulary (BNF). As expected, if propofol was more expensive and all other parameters remain the same, the cost savings with AnaConDa-S are greater at £4226.84 per sedated patient.

In relation to isoflurane, the clinical experts indicated that a typical dose per hour of isoflurane would be 8-10mls per hour (see correspondence log) which is substantially higher than the company value (3ml/hour). Using the higher median dose for isoflurane of 9mls per hour (all other values remain as EAC preferred values) the cost saving for inhaled sedation with AnaConDa-S is reduced to £3,612.19 per sedated patient.

Two-way sensitivity analysis indicated inhaled sedation delivered using AnaConDa-S remained cost saving for all comparisons when varying the unit costs of propofol and isoflurane (Figure 6).

Figure 6: Two-way sensitivity analysis with unit cost of propofol and isoflurane varied (all other values EAC preferred values)

	Unit cost of Drugs				
		AnaConDa			
Propofol	-£3,833.76	£15.00	£35.29	£50.00	£75.00
	£1.00	-£3,519.49	-£3,455.80	-£3,409.62	-£3,331.14
	£2.08	-£3,621.54	-£3,557.85	-£3,511.67	-£3,433.19
	£5.00	-£3,897.45	-£3,833.76	-£3,787.58	-£3,709.10
	£10.00	-£4,369.90	-£4,306.21	-£4,260.03	-£4,181.55
	£15.00	-£4,842.35	-£4,778.65	-£4,732.48	-£4,654.00

Additional results

The company submitted results comparing isoflurane (inhaled sedation) with midazolam (IV sedation) based on data from a published study (Krannich 2017). The key differences in this analysis were different drug acquisition

costs for midazolam and different ventilator and ICU days for both inhaled and IV sedation (appendix E).

The EAC note that clinical expert input suggests that midazolam is used primarily for sedation in children in the UK. For this reason, the EAC has investigated the impact of adjusting the dose of midazolam to account for the weight of children as well as adults and reported the results based on weights of 12kg, 24kg, 36kg, 48kg, and 60kg. The other main difference is an adjusted cost of critical care bed day costs to account for the difference in costs for adults and children (NHS reference costs).

The results of the company submitted scenario analysis with Midazolam as the comparator indicate a potential cost saving of £5,758 per patient (table 23).

Using the published data (Krannich 2017) for ventilator days and the EAC preferred inputs for costs and other parameters, the scenario analysis with Midazolam indicates a potential cost saving of £6,648.69 for inhaled sedation using AnaConDa-S.

Table 23: Inhaled Isoflurane using AnaConDa versus IV Midazolam

Model	Cost of Intervention (Inhaled isoflurane using AnaConDa-S)	Cost of Comparator (IV Midazolam)	Cost Saving
Company Scenario	£10,161.28	£15,919.55	£5,758
EAC preferred inputs (Adult patients)	£12,508.88	£19,157.57	£6,648.69
EAC preferred inputs (Pediatric Patients)	£6,883.58	£9,720.99	£2,837.41

When inputting a weight of 12kg and a cost of ICU bed days of £698.53 (see Appendix E for details) to consider the use of midazolam for sedation in children the cost savings reduced to £2,837.41 per sedated patient. According

to the BNF and BNF for children, the dose for isoflurane is the same therefore no changes were made to this variable.

In sensitivity analysis, as the weight of the patient increases, the cost of midazolam also increases due to the increased dose requirements. As there is no clinical evidence for inhaled sedation using AnaConDa in children it should be considered that the duration of ICU stays and days on ventilation may be very different for pediatric patients and this would likely have a significant impact on cost savings. In addition, the cost of pediatric ICU and training to deliver inhaled sedation for pediatric patients might be very different than for adult patients. The results of this comparison should therefore be considered with extreme caution.

9.4 *The EAC's interpretation of the economic evidence*

Broadly the EAC agreed with the model submitted by the company and made only minor changes to the submitted model, most of which resulted in favourable changes for inhaled sedation with AnaConDa-S. The key change made by the EAC was the addition of a training cost to deliver inhaled sedation with AnaConDa-S. This addition did not have a large impact the cost savings and the EAC note the costs associated with training are a conservative estimate of training costs.

The results of the economic analysis indicate that delivering inhaled sedation with isoflurane using the AnaConDa-S device is cost saving compared to IV sedation with propofol.

The key drivers of cost savings in the model were the duration of ICU stay and the duration of sedation. Based on data provided by the company from the SED001 trial, inhaled sedation using AnaConDa-S resulted in shorter mean sedation times and shorter overall ICU stays. The EAC however, caution that the duration of ICU stay and duration of sedation in the model are taken from a subset of patients in the SED001 trial – patients whose sedation approach was not switched after the 48 hour randomization period. As the

study was not powered for this subgroup analysis, the certainty of the results and the potential impact on cost savings should be considered.

Sensitivity analysis indicated that the model was robust to changes to drug doses, drug costs and to the addition of training costs with AnaConDa-S. Inhaled sedation with AnaConDa-S was cost saving provided the duration of ICU stay was at least 0.2 days shorter than with IV sedation.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The available evidence from the literature and expert clinical opinion suggests, despite none of the studies being carried out in the UK, that AnaConDa-S can be integrated into NHS clinical practice. AnaConDa-S allows for the adoption of volatile sedation in the ICU which is otherwise prevented due to the problems associated with the use of anaesthetic machines in the ICU environment. Clinical experts vary in their approach to the use of the device, either using it for a wide patient population or just those with bronchoconstriction. Nevertheless, the use of volatile sedation in the ICU is an off-label use of these agents and at least one competitor technology exists that provides a similar function to the AnaConDa-S.

As all the included studies compared the use of AnaConDa delivered volatile sedation to IV sedation, the differences of outcomes between patient groups cannot be solely attributed to the use of the device. It is not the aim of this report to suggest whether volatile sedation is more beneficial to IV sedation. With these limitations in mind the EAC brings the following points relating to the clinical evidence to the attention of the committee:

- AnaConDa-S delivered sedation offers benefit over IV sedation in terms of extubation time and wake-up time, but this is likely attributed to the volatile sedatives that AnaConDa allows to administer.
- None of the studies provided evidence on any of the pre-specified subgroups, though some experts only use the device in the context of treating patients with bronchospasm due to the properties of the volatile sedatives rather than those of the device.
- The use of volatile sedatives in the ICU is an off-label use of these pharmacological agents. Nevertheless, AnaConDa is already used in the UK ICU setting and off-label use of therapies is common in the paediatric setting. Based on the reported adverse incidents, AnaConDa-S does not present a risk that is outside of the normal range relating to the use of ICU equipment.

- The interpretation of the evidence from the SED001 trial report presents several difficulties due to how certain outcomes were presented. As such, the results of this trial should be treated with caution.

10.2 *Conclusions from the economic evidence*

Inhaled sedation with isoflurane or sevoflurane, delivered using the AnaConDa-S device is cost saving compared with IV sedation with propofol. The cost savings with sevoflurane were less than with isoflurane (£2,657.08 and £3,833.76 per sedated patient respectively) however clinical expert input suggests that isoflurane is more widely used and is therefore likely to be more relevant to NHS practice.

The key driver for the cost savings is the duration of ICU stay, including the duration of mechanical ventilation. The EAC note that the limitations of the ICU length of stay and duration of ventilation data in the model is that it is taken from a subset of patients in a clinical trial (SED001) and is therefore not powered for this outcome. The EAC sensitivity analysis indicated that if the duration of ventilation is the same for both sedation methods, provided inhaled sedation (isoflurane) with AnaConDa-S results in a 0.2-day shorter ICU stay compared with propofol, it will be cost saving. One key limitation of the model is that that no further hospital stay data are included beyond ICU stay. Published clinical data (see section 5.3) however, indicates that in the majority of the studies there is no significant difference in hospital stay between sedation methods therefore the EAC consider this will not impact the findings substantially.

Although the company submitted scenario showed that inhaled sedation with AnaConDa-S was cost saving compared with midazolam, clinical expert input indicated that midazolam is used primarily for children. EAC exploratory analysis suggest that although the savings are lower, when considering a potential pediatric population, inhaled sedation with AnaConDa remains cost saving per sedated patient (£2,837.41). There are several limitations to this analysis including:

- no clinical evidence for inhaled sedation with AnaConDa in children
- uncertainty around the cost of ICU days/ventilator days for children

- duration of ICU stays and days on ventilation may be very different for pediatric patients (data from Krannich 2017 may not be generalisable)
- cost of pediatric ICU and training to deliver inhaled sedation for pediatric patients might be very different than for adult patients

Overall, the EAC concludes that delivering inhaled sedation using the AnaConDa-S system is cost-saving compared with IV sedation with propofol but notes that the committee should consider carefully the robustness of key inputs including ICU duration and duration of mechanical ventilation.

11 Summary of the combined clinical and economic sections

AnaConDa-S is a device allowing for the delivery of volatile sedation to ICU patients managed on a mechanical ventilator. AnaConDa-S use is associated with improvements in extubation and wake-up times, but not in other outcomes of interest. Nevertheless, the evidence available does not allow one to separate any benefits arising from the use of the device from those associated with the use of volatile sedatives.

Economic analysis indicates that delivering inhaled sedation using the AnaConDa device is cost saving compared with IV sedation methods however this is driven by the duration of ICU stay and duration of ventilation.

If, based on the clinical evidence, it can be concluded that there are benefits to inhaled sedation compared with IV sedation, then using the AnaConDa-S device to deliver the inhaled sedation would be cost-saving compared with IV sedation methods.

12 Implications for research

Answering two separate questions would provide further relevant information that would guide any recommendations made with respect to the use of AnaConDa-S:

- Can volatile sedation be recommended (and if yes, then when) over IV sedation?

- Is volatile sedation delivered via AnaConDa clinically and/or economically better than other ways of delivering volatile sedation in ICU?

The first question relates to clinical practice, the outcomes associated with specific sedatives and how these relate to the needs of specific patients. This might be a question of particular importance with respect to patients with bronchoconstriction, which was a subgroup specified for this report but for which no studies were identified.

To answer the second question a comparison would have to be made between AnaConDa, competitor technologies and anaesthetic machine delivered volatile sedation in the ICU. Such a study would help to answer the question of any changes in outcome that might be specifically associated with the use of AnaConDa, separating them from any effects associated with the use of different sedative agents.

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See the NICE style guide:
https://www.nice.org.uk/corporate/ecd1/chapter/referencing-and-citations.

14 Appendices

Appendix A: Literature Searches

Appendix B: Critical Appraisal Results

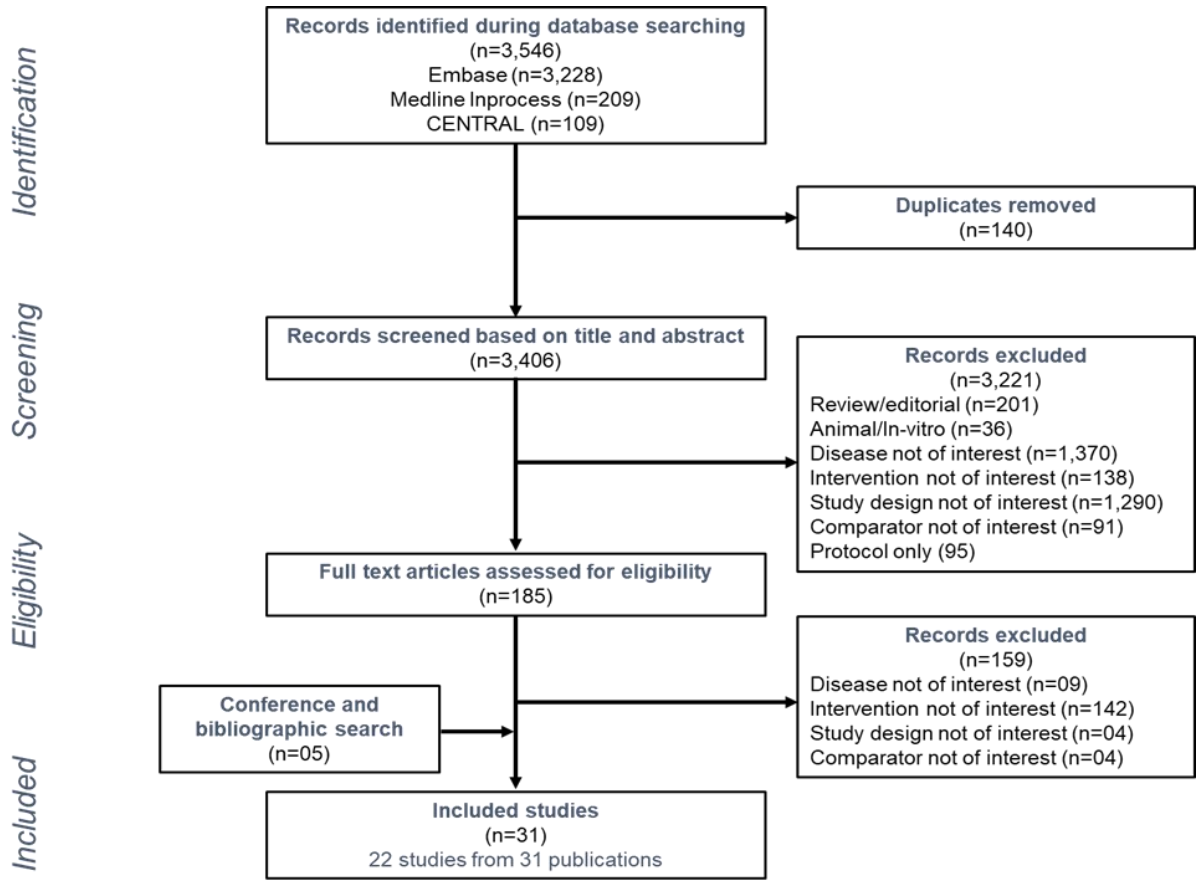
Appendix C: Conference Abstracts

Appendix A: Clinical and economic evidence identification

Company search strategy, screening criteria and process for clinical evidence

A literature search was performed in 3 databases: Medline, including Medline In Process segment; Embase and CENTRAL to include the period from database inception to 3rd August Feb 2020. The searches included a range of free text terms and indexed terms which covered a broader notion rather than the specific elements of the decision problem. That is, the population included mechanically ventilated adult patients not just those who are invasively ventilated, the intervention included various types of anaesthetics and was not specific to the AnaConda product. The key scope concepts had not been adequately captured and combined in the search strategies The searches were not restricted by language of publication but were restricted to identify randomized controlled trials only.

Company study selection for clinical evidence



Company search strategy, screening criteria and process for economic evidence

A literature search was performed in 4 databases on the 17th July 2020: Medline (2006 to 2020), including Medline In Process segment (2011 to 2020); Embase (2006 to 2020) and NHS EED (2011 to 2020). The company also submitted an updated literature search that was conducted on the 14th of April 2021. The searches included a range of free text, indexed and economic terms. The searches covered a broader notion rather than the specific elements of the decision problem. That is, the population included mechanically ventilated adult patients not just those who are invasively ventilated, the intervention included various types of anaesthetics and was not specific to the AnaConda product, the term 'Anaconda' was not included in the search strategies. The searches were not restricted by language of publication although on screening only those published in English were considered for inclusion

Company search strategy for adverse events

The company did not include any details regarding the search or identification of adverse events in the MHRA or FDA (MAUDE) regulatory databases.

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched to include the period from 1st January 2000 (to reflect issue of the CE mark) to 5th May 2021, using a range of free text terms and, where appropriate, indexed terms, the searches were not restricted by language of publication. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the FDA MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
05/05/21	Cochrane Library CDSR CENTRAL	 0 77	
29/04/21	CRD (DARE, NHS EED)	1	
29/04/21	EMBASE	118	

29/04/21	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	184	
29/04/21	PubMed	150	
05/05/21	Scopus	114	
29/04/21	Web of Science	163	
22/04/21	company website: https://www.sedanamedical.com/	22	
			457
29/04/21	MAUDE adverse events	0	
29/04/21	MHRA – search MDA & FSN	2	
29/04/21	Clinicaltrials.gov	2	9 (deduplicated against published results retrieved from database searches)
05/05/21	EU-CTR	10	

EAC Search strategies

The Cochrane Library

ID Search Hits
#1 MeSH descriptor: [Respiration, Artificial] this term only 3485
#2 (invasive ventil*):ti,ab,kw (Word variations have been searched) 4051
#3 #1 or #2 7283
#4 (anaconda):ti,ab,kw (Word variations have been searched) 57
#5 (an?esthetic conserving device):ti,ab,kw (Word variations have been searched) 57
#6 (volatile an?esthetic delivery system):ti,ab,kw (Word variations have been searched) 10
#7 MeSH descriptor: [Anesthesia, Inhalation] this term only and with qualifier(s): [instrumentation - IS] 114
#8 MeSH descriptor: [Anesthetics, Inhalation] this term only and with qualifier(s): [administration & dosage - AD] 891
#9 {OR #4-#8} 1071
#10 #3 AND #9 65
#11 (anaconda and (seda* or ventil*)):ti,ab,kw (Word variations have been searched) 43
#12 #10 OR #11 with Publication Year from 2000 to 2021, in Trials 77
#13 #10 OR #11 in Cochrane Reviews 0

CRD

Zero results for: (anaconda) IN DARE, NHSEED
1 result Results for: volatile anaesthetic delivery system) OR (anesthetic conserving device) OR (anaesthetic conserving device) OR (volatile anesthetic delivery system) IN DARE, NHSEED

EMBASE(Ovid)<1996 to 2021 April 28>

1 invasive ventilation/ (1758)
2 invasive ventil*.tw. (9331)
3 1 or 2 (10630)
4 anaconda.tw. (419)
5 an?esthetic conserving device.tw. (95)
6 volatile an?esthetic delivery system.tw. (1)
7 inhalation anesthesia/ (5425)
8 anesthetic equipment/ (2854)
9 4 or 5 or 6 or 7 or 8 (8483)
10 3 and 9 (9)
11 (anaconda and (seda* or ventil*)).tw. (129)
12 10 or 11 (135)
13 limit 12 to (human and yr="2000 -Current") (118)

INAHTA

(anaconda) OR (anesthetic conserving device) OR (anaesthetic conserving device) OR (volatile anaesthetic delivery system) OR (volatile anesthetic delivery system) FROM 2000 TO 2021: 0 results

---

MEDLINE(R) ALL (Ovid) <1946 to April 28, 2021>

1 Respiration, Artificial/ (51256)
2 invasive ventil*.tw. (4193)
3 1 or 2 (54408)
4 anaconda.tw. (252)
5 an?esthetic conserving device.tw. (58)
6 volatile an?esthetic delivery system.tw. (1)
7 Anesthesia, Inhalation/is [Instrumentation] (2673)
8 Anesthetics, Inhalation/ad [Administration & Dosage] (3659)
9 or/4-8 (6334)
10 3 and 9 (340)
11 (anaconda and (seda* or ventil*)).tw. (68)
12 10 or 11 (391)
13 exp animals/ not humans.sh. (4818943)
14 12 not 13 (345)
15 limit 14 to yr="2000 -Current" (184)

PubMed

Sedana or (Anaconda AND sedation) = 150

Scopus

((TITLE-ABS-KEY ("invasive ventil*") AND TITLE-ABS-KEY (anaconda OR "an?esthetic conserving device" OR "volatile an?esthetic delivery system"))) OR (TITLE-ABS-KEY (anaconda AND (seda* OR ventil*))) AND PUBYEAR > 1999
Result=114

Web of Science

TOPIC: (anaconda AND (seda* OR ventil*)) OR TOPIC: (an$esthetic conserving device) OR TOPIC: (volatile an$esthetic delivery system)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2000-2021
Result: 163

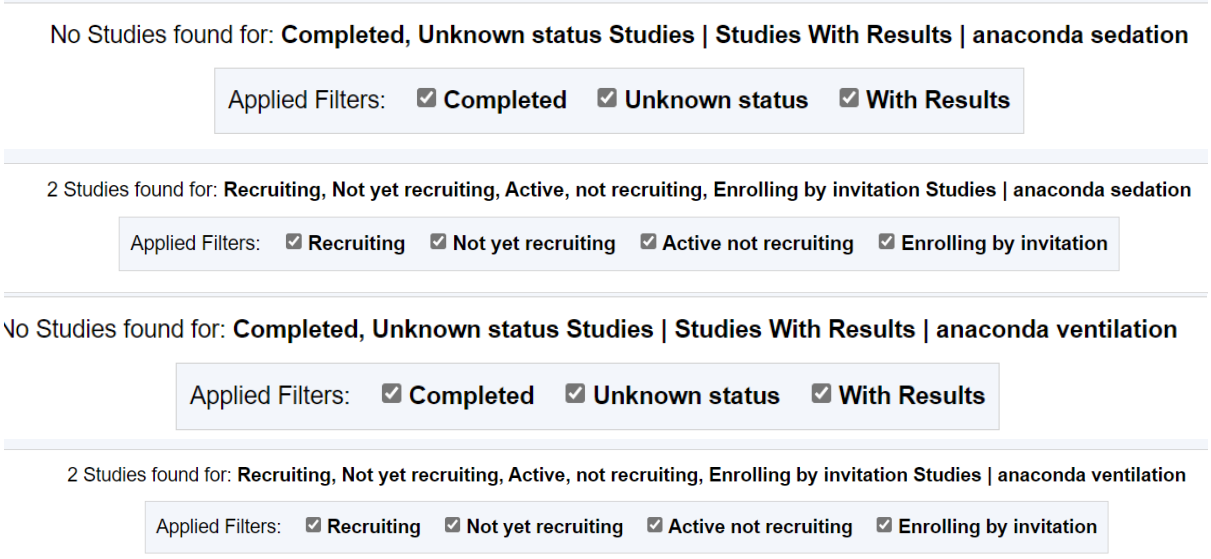
MAUDE

Searched for: Anaconda or Sedana

MHRA

Searched for: Anaconda or Sedana

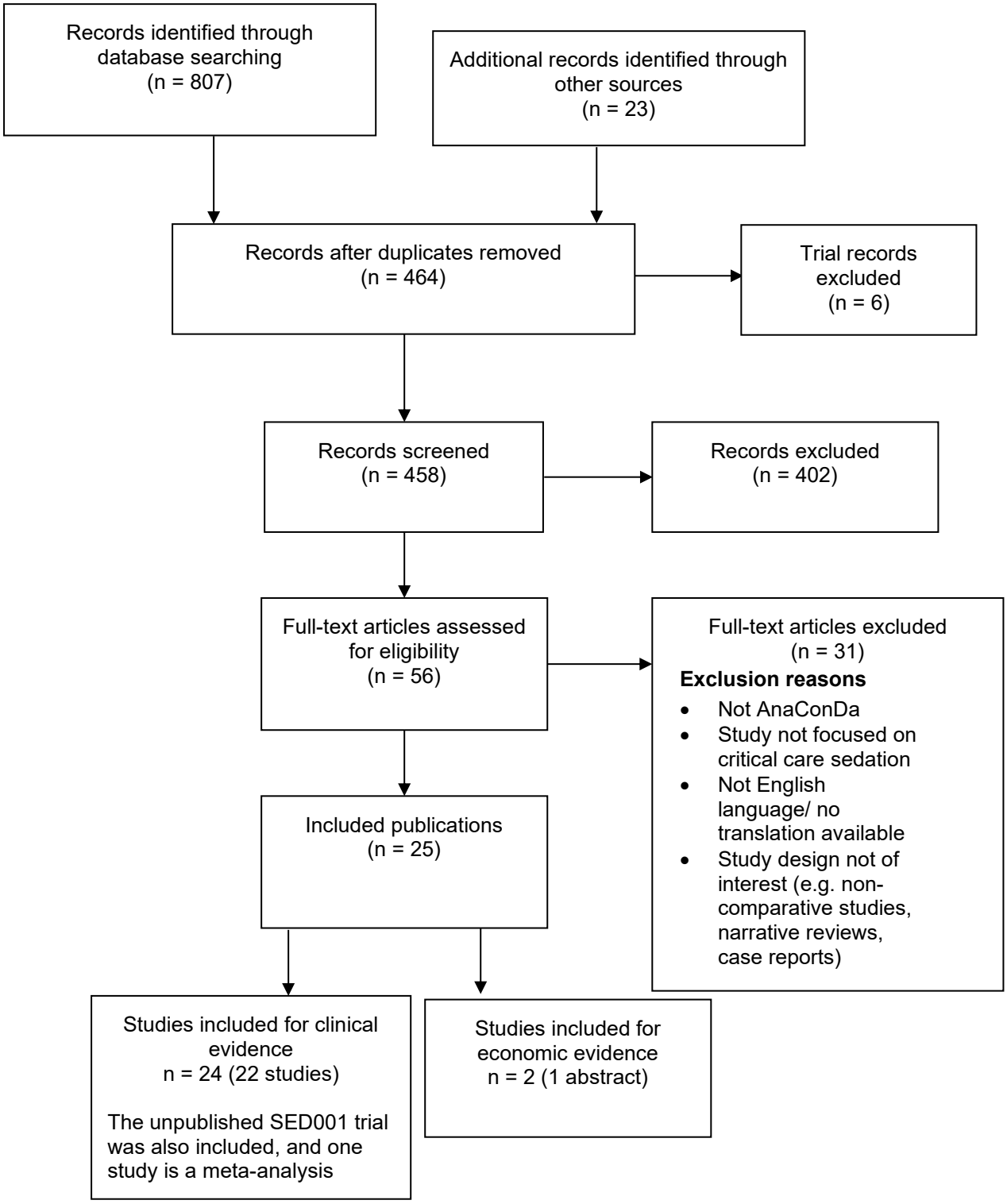
Clinical Trials.gov



EU-CTR

Anaconda [completed with results] = 1
Anaconda [ongoing] = 5

EAC study selection



Appendix B: Critical Appraisal Results

Randomised Controlled Trials

All the RCTs were assessed using the:

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group
Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	**Guerrero Orriach JL, Galán Ortega M, Ramirez Aliaga M, et al. Prolonged sevoflurane administration in the off-pump coronary artery bypass graft surgery: beneficial effects. Journal of Critical Care. 2013 Oct;28(5):879.e13-8. DOI: 10.1016/j.jcrc.2013.06.004.**

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	1) Sevoflurane-sevoflurane (SS): intraoperative and postoperative administration of sevoflurane	Comparator:	2. Sevoflurane-propofol (SP) intraoperative administration of sevoflurane and postoperative propofol. 3. Propofol-propofol (PP): intraoperative and postoperative administration of propofol.

Specify which outcome is being assessed for risk of bias	Primary outcome not specified. N-terminal pro-brain natriuretic peptide and troponin I
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	There were significant differences between group SS and the other 2 groups in the levels of Nterminal pro-brain natriuretic peptide (SS [501 ± 280 pg/mL] compared with SP [1270 ± 498 pg/mL] and PP [1775 ± 527 pg/mL] [P b .05]) and troponin I (SS [0.5 ± 0.4 ng/mL] compared with SP [1.61 ± 1.30 ng/mL] and PP [2.27 ± 1.5 ng/mL] [P b .05]) and a lower number of inotropic drugs.

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application

☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	No information. (Statement that patients were randomised but no further information)	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No Information.	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	There were no significant differences in the epidemiological risk, anesthetic risk, myocardial function, preoperative medication, surgery times, and number of grafts between groups (Table 1).	N
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Patient allocation was randomized but not concealed to clinical caregivers. For technical reasons (AnaConDa device), itwas impossible to blind our trial completely. Randomization to anesthetic technique was done preoperatively, but allocation was visible to anesthesiologists in the operating room and intensive care, due to the different drug administration devices. Thus, our study was only blinded with regard to data analysis.	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Deviations not reported	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No evidence that patients removed from analysis, although n in each analysis not specifically reported.	PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	No information on extent of missing data. Ns not given.	NI

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NI
Risk-of-bias judgement		High
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Surrogate marker used but probably appropriate.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Based on blood test	N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized	Very little information analysis	NI

before unblinded outcome data were available for analysis?		
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.	High risk
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Hanafy, M. A. (2005). Clinical evaluation of inhalational sedation following coronary artery bypass grafting. *EGYPTIAN JOURNAL OF ANAESTHESIA*, *21*(3), 237.

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Comparator:
Isoflurane based sedation regimen using AnaConDa	Conventional intravenous midazolam sedation

Specify which outcome is being assessed for risk of bias	Primary outcome not specified. Wake up times.

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Time to extubation was 15.2 (5.3 SD) min vs 120.1 (30.3 SD) min.

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Sealed envelope	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Discussion says not double blind	PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Appears to be ITT	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns

Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards

		null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Authors comment that Ramsey scale is not very sensitive	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		Y
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.	High
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Hellström, J., Öwall, A., Bergström, J., & Sackey, P. V. (2011). Cardiac outcome after sevoflurane versus propofol sedation following coronary bypass surgery: a pilot study. Acta anaesthesiologica Scandinavica, 55(4), 460–467. https://doi.org/10.1111/j.1399-6576.2011.02405.x And Hellström, J., Öwall, A., & Sackey, P. V. (2012). Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery. Scandinavian cardiovascular journal : SCJ, 46(5), 262–268. https://doi.org/10.3109/14017431.2012.676209

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Sevoflurane via AnaConDa Comparator: Propofol

Specify which outcome is being assessed for risk of bias	cTnT 12 h post-operatively
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	no statistically significant difference between groups in the primary endpoint cTnT values at 12 h post-operatively

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Full details not provided, no information on how sequence was generated. 'A nurse in the ICU drew a sealed envelope with a treatment code (sevoflurane or propofol)'.	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No baseline statistical testing presented in Hellstrom 2011. Differences in pre-op cTnT, statin treatment, MI. Other variables presented in Hellstrom 2012 which didn't show statistical differences.	PY
Risk-of-bias judgement		Low / High / some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	The statistical analyses were performed according to intention to treat (one patient failed to receive a randomized intervention with sevoflurane)	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA

Risk-of-bias judgement		low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Only 1 didn't receive intervention	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	primary endpoint cTnT was measured in micrograms per liter using a third-generation assay (Roche Diagnostics AB, Bromma, Sweden)	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Study not double blinded but no information if assessors were blind, however as an objective outcome measure not an issue.	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours

		comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Clinical trial report is consistent with reported outcome	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Jabaudon M, Boucher P, Imhoff E, Chabanne R, Faure JS, Roszyk L, Thibault S, Blondonnet R, Clairefond G, Guérin R, Perbet S, Cayot S, Godet T, Pereira B, Sapin V, Bazin JE, Futier E, Constantin JM. Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. Am J Respir Crit Care Med. 2017 Mar 15;195(6):792-800. doi: 10.1164/rccm.201604-0686OC. PMID: 27611637.

Study design

X Individually-randomized parallel-group trial
 Cluster-randomized parallel-group trial
 Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: midazolam Comparator: sevoflurane

Specify which outcome is being assessed for risk of bias	PaO2/FIO2 Ratio
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Sevoflurane mean and SD 250 (56) Midazolam 16 (59) p=0.04 in abstract and also table 2

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
 to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

 occurrence of non-protocol interventions
 failures in implementing the intervention that could have affected the outcome
 non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
 Trial protocol
 Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
 Company-owned trial registry record (e.g. GSK Clinical Study Register record)
 "Grey literature" (e.g. unpublished thesis)
 Conference abstract(s) about the trial
 Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
 Research ethics application
 Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
 Personal communication with trialist
 Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Computer generated but no details regarding allocation concealment method	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant differences between the groups	N
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open labelled	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards

		null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Available for all participants	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	More information given in online supplement	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Analysis of the samples performed by blinded assessors	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes outcome stated in clinical trial registry data	Y

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Jerath A, Beattie SW, Chandy T, Karski J, Djaiani G, Rao V, Yau T, Wasowicz M, on behalf of the Perioperative Anesthesia Clinical Trials Group. Volatile-Based Short-Term Sedation in Cardiac Surgical Patients: A Prospective Randomized Controlled Trial. Clinical Investigations. 2015: (43) 5 1062- 1069

Study design

X Individually-randomized parallel-group trial
 Cluster-randomized parallel-group trial
 Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Inhaled volatile anesthetic agents (isoflurane or sevoflurane) via Anaconda	Comparator:	IV propofol

Specify which outcome is being assessed for risk of bias	Extubation times (not primary outcome and study therefore not powered for this outcome)
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3 Readiness to extubation time, min (range) volatile 135 (95-200), propofol 215 (150-280) p<0.001 Extubation time, min (range) volatile 182 (140-255), propofol 292 (210-420) p<0.001

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
 to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

 occurrence of non-protocol interventions
 failures in implementing the intervention that could have affected the outcome
 non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
 Trial protocol
 Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
 Company-owned trial registry record (e.g. GSK Clinical Study Register record)
 "Grey literature" (e.g. unpublished thesis)
 Conference abstract(s) about the trial
 Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
 Research ethics application
 Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
 Personal communication with trialist
 Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	States randomised but no information on how they were randomised	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information provided	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Appear similar except rate of diabetes differs between group 18% vs 37%	PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	States was an open label trial	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	3 in propofol group did not receive intended intervention, 1 in volatile group	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Analysis of those who received intervention and not of those that were allocated 157 patients were subsequently randomized to receive a study intervention: 78 within the propofol and 79 within the volatile groups. A total of 141 patients (74 propofol and 67 volatile) completed the trial and formulated the basis of our data analysis.	N
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Only 4 in total so minimal	PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	11 discontinued treatment in the volatile group and 1 in the propofol group no data was given for these participants except reason for discontinuation, and 4 did not receive either intervention after randomisation. 10% of randomized group missing and a continuous outcome so probably marginal impact	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No data given	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	This is a subanalysis performed from a study originally powered to assess cardiac outcomes in participants. Time to extubation specified as outcome on trls website	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Mesnil M, Capdevila X, Bringuier S, Trine P-O, Falquet Y, Charbit J, Roustan J-P, Chanques G, Jaber S. Long-term sedation in intensive care: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. Intensive Care Med (2011) 37:933-941

Study design

X Individually-randomized parallel-group trial
□ Cluster-randomized parallel-group trial
□ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Inhaled sevoflurane	Comparator:	Intravenous propofol or midazolam

Specify which outcome is being assessed for risk of bias	Wake-up times and extubation delay from termination of sedative administration
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Wake up times and extubation times S (18.6 +/11.8 and 33.6 +/- 13.1 min), P (91.3 +/- 35.2 and 326.11 +/- 360.2 min) and M (260.2 +/- 150.2 and 599.6 +/- 586.6 min) p<0.01 in the S than in the P and M group. Data given in abstract and Figure 3

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
□ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

□ occurrence of non-protocol interventions
□ failures in implementing the intervention that could have affected the outcome
□ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
□ Trial protocol
□ Statistical analysis plan (SAP)
□ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
□ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
□ "Grey literature" (e.g. unpublished thesis)
□ Conference abstract(s) about the trial
□ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
□ Research ethics application
□ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
□ Personal communication with trialist
□ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Performed by sealed letters no more information was provided on sequence generation	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	No blinding reported	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	3 participants in P and 3 participants in the M group had loss of follow up data as were unable to adjust sedative drugs but text in flow diagram 'heavy burden' is slightly confusing but unlikely to be due to trial context	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		N/A
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Didn't include those that were randomized excluded those lost to follow-up	N
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Possibly yes as 6 not analyzed in each of P and M groups	PY
Risk-of-bias judgement		High
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		PN
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		PN
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware		Y

of the intervention received by study participants?		
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Not available	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Röhm KD, Wolf MW, Schöllhorn T, Schellhaass A, Boldt J, Piper SN. Short-term sevoflurane sedation using the Anaesthetic Conserving Device after cardiothoracic surgery. Intensive Care Med. 2008 Sep;34(9):1683-9. doi: 10.1007/s00134-008-1157-x. Epub 2008 May 24. PMID: 18500419.

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: sevoflurane Comparator: propofol

Specify which outcome is being assessed for risk of bias	Extubation time from end of sedation
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	22 vs 151 minutes sevoflurane vs propofol p<0.002 abstract and figure 2

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options

1.1 Was the allocation sequence random?	Sealed envelopes but no details on randomisation sequence	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Simple demographics in table 1 but no p values	PN
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	States single blinded but no more information given as to who, more likely care givers	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Not clear 102 patients were excluded due to exclusion criteria or violation of protocol, no study flow diagram but not clear if this after randomisation but looking at numbers for power calculation (n=33) likely that those excluded were before randomisation.	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Unclear as no study flow diagram but looks as if numbers randomized were same as analysed	PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Probably yes by deciphering text for power calculation, and indicated numbers who were randomized and analyzed.	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Single blinded but not clear who	PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Consistent with clinical trial registry	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Some concern
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med 2004:32(11), 2241-2246

Study design

X Individually-randomized parallel-group trial
 Cluster-randomized parallel-group trial
 Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Inhaled isoflurane with Anaconda Comparator: IV midazolam

Specify which outcome is being assessed for risk of bias	Wake up time from termination of sedation administration (time to extubation) and proportion of time within a predefined desired interval on a sedation scale
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3 Isoflurane time to extubate minutes mean 10 SD 5, Midazolam mean 250 SD 270 Isoflurane Time to follow verbal commands minutes mean 10 SD 250 SD 270, Midazolam 110 SD 130

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
 to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

 occurrence of non-protocol interventions
 failures in implementing the intervention that could have affected the outcome
 non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
 Trial protocol
 Statistical analysis plan (SAP)
 Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
 Company-owned trial registry record (e.g. GSK Clinical Study Register record)
 "Grey literature" (e.g. unpublished thesis)
 Conference abstract(s) about the trial
 Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
 Research ethics application
 Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
 Personal communication with trialist
 Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Just states randomized	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No obvious differences	N
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	States single blinded but not clear who, but later on states that double blinding not feasible	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	! midazolam sedated patient had data excluded as did not wake up during the study period	PY
2.7 If N/PN/NI to 2.6: Was there potential for a		NA

substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors		Y

aware of the intervention received by study participants?		
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Measured response to verbal commands such as squeeze hand	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No CT.gov record or publicly available plan to check	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	SED001: A randomised, controlled, open-label study to confirm the efficacy an of sedation with isoflurane in invasively ventilated ICU patients using the AnaC administration system https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004551-67/results Trial report supplied to Cedar HERE

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Comparator:
Isoflurane administered by inhalation via AnaConDa	Propofol infusion

Specify which outcome is being assessed for risk of bias	[redacted]
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	[redacted]

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
"Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
X Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist

X	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	[redacted]	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	[redacted]	N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned	[redacted]	Y

intervention during the trial?	[redacted]	
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	[redacted]	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	[redacted]	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of		Y / PY / PN / N / NI

participants' assigned intervention during the trial?		
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA

Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	**Comments**	**Response options**
4.1 Was the method of measuring the outcome inappropriate?	[redacted]	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	[redacted]	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	[redacted]	N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	[redacted]	Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Soro M, Gallego L, Silva V, Ballester MT, Llorens J, Alvarino A, Garcia-Perez ML, Pastor E, Aguilar G, Marti FJ, Carratala A, Belda FJ. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: a double blind randomised study. Eur J Anaesthesiol 2012; 29:561-569

Study design

X Individually-randomized parallel-group trial
 Cluster-randomized parallel-group trial
 Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Sevoflurane inhaled Comparator: propofol

Specify which outcome is being assessed for risk of bias	Myocardial markers
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	TnI, myoglobin, CK-MB and NT-proBNP values were not significantly different between the study groups at anytime points. Results given in Figure 2

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
 to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

 occurrence of non-protocol interventions
 failures in implementing the intervention that could have affected the outcome
 non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
 Trial protocol
 Statistical analysis plan (SAP)
 Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
 Company-owned trial registry record (e.g. GSK Clinical Study Register record)
 "Grey literature" (e.g. unpublished thesis)
 Conference abstract(s) about the trial
 Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
 Research ethics application
 Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
 Personal communication with trialist
 Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Random number table generator, sealed opaque envelopes	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant differences	N
Risk-of-bias judgement		low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	First investigator carried out clinical preparations and adjustments of the drug infusion rates following the anaesthetic and sedation protocols. A second investigator blinded to the assigned group was in charge of data collection and clinical management	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	2 in propofol group did not undergo surgery, excluded from analysis but minimal number	N
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		N
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	2 in propofol group did not undergo surgery, excluded from analysis but minimal number	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N

Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Steurer, M. P., Steurer, M. A., Baulig, W., Piegeler, T., Schläpfer, M., Spahn, D. R., ... & Beck-Schimmer, B. (2012). Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. Critical Care, 16(5), 1-9.

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Propofol sedation Comparator: Sevoflurane sedation

Specify which outcome is being assessed for risk of bias	Troponin at POD1.
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Concentration of troponin T as the most sensitive marker for myocardial injury at POD1 was significantly lower in the sevoflurane group compared with the propofol group (unadjusted difference, -0.4; 95% CI, -0.7 to -0.1; P < 0.01; adjusted difference, -0.2; 95% CI, -0.4 to -0.02; P = 0.03, respectively).

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Randomization was computer generated with prestratification for the following surgery groups: (a) aortic valve surgery, (b) mitral valve surgery, and (c) combined procedures with coronary artery bypass grafting (CABG) or replacement of the ascending aorta. The envelope was opened by an investigator at the end of the case. Anesthesiologists and surgeons were blinded to the intervention	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Participants were not awake.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to		NA

have affected the outcome?		
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	They carried out a per-protocol not ITT. 117 randomised but 46+56 analysed. According to the RoB tool…"Both intention-to-treat (ITT) analyses and modified intention-to-treat (mITT) analyses excluding participants with missing outcome data should be considered appropriate". The paper states that "We did not include patients in the analyses who were extubated early and who could not be sedated appropriately, because we did not collect outcome data for these patients" so this meets definition of mITT.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
2.4. [If applicable:] Were there failures in implementing the intervention that could		NA

have affected the outcome?		
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	We did not include patients in the analyses who were extubated early and who could not be sedated appropriately, because we did not collect outcome data for these patients.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options

4.1 Was the method of measuring the outcome inappropriate?	An important aspect of our study that must be considered is the fact that only biomarkers were analyzed. If such positive results would claim the potential of being translated into clinical routine, similar findings from additional studies would be necessary. Such trials would require large numbers of patients. Nevertheless, using biomarkers is certainly a reliable approach for a first clinical trial, which allows linking the finding with current preclinical work including	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Data analyst was masked for group assignment when performing the statistical analyses. Analysis plan not found.	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		

5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		PN
5.3 ... multiple eligible analyses of the data?		PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Türktan, M., Güleç, E., Hatipoğlu, Z., Ilgınel, M. T., & Özcengiz, D. (2019). The Effect of Sevoflurane and Dexmedetomidine on Pulmonary Mechanics in ICU Patients. *Turkish journal of anaesthesiology and reanimation*, *47*(3), 206.

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	0.5%-1% sevoflurane (4-10 mL h−1) was used by an Anaesthetic Conserving Device	Comparator:	iv dexmedetomidine infusion (1 µg−1 kg−1 10 min−1 loading and 0.2-0.7 µg−1 kg−1 h−1 maintenance)

Specify which outcome is being assessed for risk of bias	No primary outcome Arterial blood gas analysis, airway resistance, positive end-expiratory pressure (PEEP), frequency, tidal volume (TV), peak airway pressure (Ppeak), static pulmonary compliance and end-tidal CO2 values were recorded at baseline, 1, 3, 6, 9, 12 and 24 h.
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Many variables reported

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Patients were randomly divided into two groups according to a computer-generated random number list.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Small numbers mean imbalanced	N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	No information on blinding.	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NI

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All patients appear to analysed in their randomised group	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	These are makers rather than clinical outcomes.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the		PY

outcome have been influenced by knowledge of intervention received?		
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Many comparisons without correction.	Y
5.3 ... multiple eligible analyses of the data?		Y
Risk-of-bias judgement		High
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	The study is judged to be at **high risk of bias** in at least one domain for this result.	High

Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Non-RCT comparative studies
JBI Critical Appraisal Checklist for Case Series

Reviewer Sarah Kotecha

Date 20/5/21

Author Bellgardt et al. Year 2016

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	X	☐
Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
Did the case series have complete inclusion of participants?	X	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal comments

Case series with following caveats:
Question 2 - Chose 96 h duration of mechanical ventilation as a criteria for inclusion.
Question 5 – although stated that ‘all patients were eligible for inclusion’ only 2 patients could be sedated with anaconda simultaneously so unlikely that consecutive inclusion.

NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)

Bomberg 2018 Criteria	Yes, No, Other (unclear, not reported, not applicable)
1. Was the study question or objective clearly stated?	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No – none presented
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear -small sample which might not be representative of other ICU patients.
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Not reported
5. Was the sample size sufficiently large to provide confidence in the findings?	No – 10 patients
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes – well described

Bomberg 2018 Criteria	Yes, No, Other (unclear, not reported, not applicable)
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Not applicable – all received same treatment and outcomes not subjective
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Not applicable
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Not applicable, not set up as time series but 2 time points with each device version in observation period
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Not applicable

Overall assessment: Cross over design with no control group. No eligibility criteria presented and not able to determine how representative the sample is to other ICU patients due to small sample size.

JBI Critical Appraisal Checklist for cohort studies

Author____Foudraine 2021

	Yes, No, Unclear, Not applicable
1. Were the two groups similar and recruited from the same population?	Yes - Between January 2014 and October 2019, 406 patients admitted to ICU were retrospectively screened for eligibility.
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes - Intervention administered as per protocol
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	Yes
5. Were strategies to deal with confounding factors stated?	Yes - multivariate logistic Cox regression analysis with corrections for the confounding variables including time to ROSC, amount of sedative used, and lowest body temperature
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear – could delirium develop before administering anaesthetics
7. Were the outcomes measured in a valid and reliable way?	Unclear – noted that CAM-ICU has drawbacks
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes – propensity matched
10. Were strategies to address incomplete follow up utilized?	Not applicable
11. Was appropriate statistical analysis used?	Yes

Overall appraisal comments: Retrospective cohort, unclear if delirium could've developed before administering anaesthetics and authors note that the CAM-ICU method to measure delirium may not be appropriate for all patients.

JBI Critical Appraisal Checklist for cohort studies

Author____Jung 2020 (conducted by HM)

	Yes, No, Unclear, Not applicable
1. Were the two groups similar and recruited from the same population?	Yes
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	Yes
5. Were strategies to deal with confounding factors stated?	Not applicable – no differences at baseline
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Not applicable
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes
10. Were strategies to address incomplete follow up utilized?	Not applicable
11. Was appropriate statistical analysis used?	Yes

Overall appraisal comments: appraisal of retrospective element of cohort study comparing volatile sedation and propofol sedation.

JBI Critical Appraisal Checklist for cohort studies

Reviewer Judith White Date 8th June 2021

Author Krannich et al. Year 2017 Record Number N/A

	Yes	No	Unclear	Not applicable
12. Were the two groups similar and recruited from the same population?	X	☐	☐	☐
13. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
14. Was the exposure measured in a valid and reliable way?	X	☐	☐	☐
15. Were confounding factors identified?	X	☐	☐	☐
16. Were strategies to deal with confounding factors stated?	X	☐	☐	☐
17. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
18. Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
19. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
20. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
21. Were strategies to address incomplete follow up utilized?	X	☐	☐	☐
22. Was appropriate statistical analysis used?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for cohort studies

Author____Marcos-Vidal 2014 (conducted by HM)

	Yes, No, Unclear, Not applicable
1. Were the two groups similar and recruited from the same population?	Yes
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	Yes – no differences in baseline characteristics
5. Were strategies to deal with confounding factors stated?	N/A
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	No - but measured, although at admission before surgery there was statistical significant difference in TnT.
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes - once eligibility applied
10. Were strategies to address incomplete follow up utilized?	N/A
11. Was appropriate statistical analysis used?	Yes

Overall appraisal comments: cohort study, appropriate selection. However note that the troponin levels (main outcome) were significantly different at baseline between groups.

NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)

Marcos-Vidal 2020 (appraised by HM) Criteria	Yes, No, Other (unclear, not reported, not applicable)
1. Was the study question or objective clearly stated?	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear – small sample (n=23) who may not be representative.
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes – sample size calculated
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes

Marcos-Vidal 2020 (appraised by HM) Criteria	Yes, No, Other (unclear, not reported, not applicable)
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No – data collected manually by 3 investigators
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes – those excluded didn't met eligibility criteria
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No – but 2 time points with each device version in observation period
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Not applicable

Overall assessment: no control group with comparison made in same patient group, small sample may not be representative of all patients, data collected manually so not blinded, 2 data points for each device which may not be sufficient.

JBI Critical Appraisal Checklist for cohort studies

Author____Meiser 2018 (conducted by HM)

	Yes, No, Unclear, Not applicable
12. Were the two groups similar and recruited from the same population?	Yes
13. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
14. Was the exposure measured in a valid and reliable way?	Yes
15. Were confounding factors identified?	Yes
16. Were strategies to deal with confounding factors stated?	N/A – no differences in baseline characteristics
17. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	N/A
18. Were the outcomes measured in a valid and reliable way?	Yes
19. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
20. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes
21. Were strategies to address incomplete follow up utilized?	N/A
22. Was appropriate statistical analysis used?	Yes

Overall appraisal comments: retrospective cohort study, small sample (n=38) which may not be representative, no differences in baseline characteristics.

JBI Critical Appraisal Checklist for cohort studies

Author____Staudacher 2018 (conducted by HM)

	Yes, No, Unclear, Not applicable
1. Were the two groups similar and recruited from the same population?	Yes but time periods differed for propofol group and isoflurane as there was a change in ICU protocol but propofol could still be used.
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	Yes
5. Were strategies to deal with confounding factors stated?	Yes – propensity score matching and comparable to whole cohort
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Not applicable
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes
10. Were strategies to address incomplete follow up utilized?	Not applicable
11. Was appropriate statistical analysis used?	Yes

Overall appraisal comments: retrospective cohort study, time periods differed for propofol group and isoflurane as there was a change in ICU protocol but propofol could still be used. Propensity score matching was used and comparable to whole cohort.

Appendix C: Conference abstracts

Study & population	Study design, aim & participants	Key findings & authors' conclusions
Badenes (2012) – abstract #0577 Patients in a Surgical ICU after neurosurgery	Prospective observational case series (consecutive) Aim: to assess the safety and efficacy of using the AnaConDa with sevoflurane while maintaining sedation after neurosurgery. n=32	Duration of sedation = 78±13 minutes Time to awakening = 4.4 minutes (range 1-18 minutes) Routine SICU postoperative neurosurgical patients sevoflurane sedation with the AnaConDa is easily feasible, effective, safe, and has a relatively short awakening period.
Bösel (2011) – poster #65 People with cerebrovascular neurocritical care conditions (ischaemic stroke, intracerebral or subarachnoid haemorrhage)	Observational case series Aim: to measure the impact of volatile sedation with isoflurane (delivered via AnaConDa) on cerebral circulation, oxygenation and pressure (mean arterial and cerebral perfusion). n=20	Sedation goals were reached with no serious complications. Intracranial pressure remained below the critical value of 20mmHg. Volatile sedation in 20 cerebrovascular neurocritical care patients with isoflurane seemed safe and feasible in the switch period and over an observation time of 12 hours.
Knafelj (2017a) - #0234 People admitted to ICU with respiratory failure because of severe asthma	Retrospective analysis of consecutive patients Aim: to compare bronchodilatory add-on effects of sevoflurane and propofol to fenoterol/ipratropium. Sevoflurane (AnaConDa) group n=10 Propofol group n=10	Increase in lung compliance was seen only in the sevoflurane group (p=0.01). When used in combination with fenoterol/ ipratorpium, sevoflurane ensures sufficient sedation level while decreasing PEEPi (intrinsic positive end-expiratory pressure) and resistance in severe asthma.
Knafelj (2017b) - #0261 Mechanically ventilated patients in the ICU	Prospective case series, with consecutive patients being treated with different infusion rates. To report volatile anesthetic consumption with the new AnaConDa-S, and compare infusion rates and sevoflurane consumption with the original AnaConDa device. n=20	In order to achieve 0.5 vol% sevoflurane concentration, higher infusion rates of sevoflurane are needed with AnaConDa-S compared with the original AnaConDa. At 1 vol% and minute ventilation ≥ 9 L, sevoflurane consumption is comparable.

Study & population	Study design, aim & participants	Key findings & authors' conclusions
Koroša (2015) Adults sedated with sevoflurane in a medical ICU	Retrospective case series (review of medical records) Aim: to describe the authors' experience with sevoflurane (delivered via AnaConDa); to outline which patients were sedated with sevoflurane; and to present the safety profile. n=61	Duration of sedation = 3.6±2.3 days Discontinuation due to worsening ventilation (11%); unexpected awakening (9%); symptoms of delirium after sedation (13%). Sevoflurane was considered an appropriate sedation agent in a diverse group of patients. Advantages over IV sedation could be more pronounced in some patient groups (e.g. resuscitation after cardiac arrest). The safety profile of sevoflurane sedation was comparable with IV sedation.
Meiser (2020) - #001315 Adult invasively ventilated patients with clinical need for sedation	Phase III multicentre RCT Aim: To evaluate the efficacy and safety of isoflurane via AnaConDa for up to 48 hours sedation in invasively ventilated patients Intervention: Isoflurane sedation using AnaConDa Comparator: IV propofol n=301. The authors did not report how many patients were in each group, nor the randomisation ratio.	The percentage of time patients were sedated in the target RASS (Richmond Agitation-Sedation Scale) range without rescue sedation was similar for the isoflurane and propofol groups ([CI] 90.7 [86.8-94.6%] vs 91.1 [87.2, 95.0]). The preliminary results indicate that isoflurane (delivered via AnaConDa) is efficacious as a primary sole sedative, in the same efficacy range as propofol.
Menzel (2015) #p-225 Children (age 2-30 months) with prolonged or difficult sedation following congenital cardiac surgery.	Retrospective case series (review of electronic medical records) Aim: to analyse spontaneous breathing and safety of isoflurane sedation delivered using AnaConDa. n=12	Median duration of sedation = 7.9 days Patients with >50% spontaneous breathing = 29% (after 6 hours), and 50% (after 18 hours). Volatile sedation provides initiation of effective spontaneous breathing and timely extubation in patients with congenital heart disease and prolonged or difficult sedation. Haemodynamics remained stable, fluoride levels were low during and after therapy. There were no relevant side effects.

<table>
<tr><th>Study & population</th><th>Study design, aim & participants</th><th>Key findings & authors' conclusions</th></tr>
<tr><td>Mikhael (2011)

People requiring ventilation and sedation in ICU following elective aortocoronary bypass surgery</td><td>Pilot RCT

Aim: to compare sedation using volatile anaesthetics (delivered via AnaConDa) with IV propofol.

Propofol group n=34

Volatile sedation group:
- Sevoflurane n=16
- Isoflurane n=21</td><td>Patients sedated using volatile agents had shorter extubation time than those sedated using propofol (p<0.005), but were more likely to require intraoperative noradrenaline (p<0.05).

Firm conclusions cannot be drawn from this ongoing pilot study. Administration of volatile sedation with the use of the AnaConDa device is a feasible option, which seems to facilitate rapid extubation. These pilot data did not find any evidence of clinically significant cardioprotective properties.</td></tr>
<tr><td>Pavcnik-Arnol (2014)

Children in a paediatric ICU with tolerance to IV sedatives</td><td>Case series

Aim: to report experience with sevoflurane sedation delivered via AnaConDa in children with tolerance to IV sedatives.

n=21

Sevoflurane placement in AnaConDa:
- inspiratory limb n=16
- at Y-piece n=5</td><td>Percentage of time (note: columns do not add to 100%):
<table><tr><th>Level of sedation</th><th>AnaConDa inspiratory limb</th><th>AnaConDa Y-piece</th></tr><tr><td>Adequate</td><td>72%</td><td>75%</td></tr><tr><td>Excessive</td><td>15%</td><td>40%</td></tr><tr><td>Inadequate</td><td>3%</td><td>0%</td></tr></table>
AEs: Decreased mean arterial pressure >15% (3); choreoathetoid movements (4); hallucinations (1).

Sevoflurane delivered by AnaConDa is effective for sedation of critically ill children with tolerance to IV sedatives, especially during weaning from mechanical ventilation.</td></tr>
<tr><td>Redaelli (2013)

Ventilator-dependent ICU patients with severe Acute Respiratory Distress Syndrome (ARDS)</td><td>Retrospective case series

Aim: to report experience in the use of isoflurane (delivered via AnaConDa) for prolonged sedation in patients with severe ARDS.

n=15

Reasons for isoflurane administration:
- High level of common sedative drugs (n=9)
- Use of ≥2 hypnotic drugs (n=5)
- Hypertriglyceridemia (n=1)</td><td>Isoflurane sedation duration = 5.6±1.8 days

No alteration in renal function or haemodynamic instability was recorded. Precautionary cessation occurred due to concomitant alteration of liver function (n=1) and suspected seizures (n=1).

AnaConDa is a device that allows a safety and easy administration of inhaled anesthetics in the ICU. It could be especially useful in case of an inadequate sedation plan; e.g. in patients with a history of drug abuse or young severe ARDS patients that required deep sedation and paralysis for a long period.</td></tr>
</table>

Study & population	Study design, aim & participants	Key findings & authors' conclusions
Trieschmann (2014) Children with difficult sedation requiring a rescue treatment	Retrospective case series Aim: to evaluate the safety of sedation with isoflurane (delivered via AnaConDa) in children, with particular focus on cardiovascular stability and fluoride levels. n=16	Isoflurane sedation duration = 7.3±4.5 days Isoflurane concentration increased over time. No significant changes in blood pressure or fluoride levels. Sedation with volatile sedatives allows significant reduction of other sedatives and analgesics; cardiovascular stability is provided and fluoride levels do not exceed toxic values.
Troubleyn (2016) People with severe Acute Respiratory Distress Syndrome (ARDS) or intractable cardiogenic shock being treated using extracorporeal membrane oxygenation (ECMO)	Retrospective review Aim: to assess the efficacy and safety of prolonged use of volatile sevoflurane (infused via AnaConDa) in haemodynamically unstable patients under ECMO. n=21	Initiation of sevoflurane allowed immediate cessation of IV sedation and curarization. Duration of treatment = 13±9 days Survival = 12/21 (57%) No adverse events were recorded. In this population, prolonged sedation with volatile sevoflurane is an effective, well-tolerated, and safe alternative to "classic" IV midazolam and propofol-based sedation.
Walczak (2019) Critically ill patients (median age 59 years)	Substudy of the VALTS prospective RCT (n=60) Aim: to determine whether the use of volatile anaesthetics for sedation is associated with long-term cognitive impairment (as compared to IV sedation). Isoflurane sedation via AnaConDa n=40 IV propofol and/or midazolam sedation n=20	21/36 patients in the substudy received isoflurane sedation via AnaConDa. Duration of sedation = 4.1±3.4 days Incident delirium (p=0.51): - Intervention = 42.1% - Comparator = 53.9% Unimpaired cognitive performance at 3 month follow-up (p=0.33): - Intervention = 41.1% - Comparator = 22.2% The use of volatile anaesthetics for sedation in critically ill patients may be associated with a lower incidence of delirium and a lower proportion of patients with long-term cognitive impairment.

Study & population	Study design, aim & participants	Key findings & authors' conclusions
Wasowicz (2012) People undergoing elective cardiac surgery (coronary artery bypass graft)	Prospective randomised evaluator-blinded study Aim: to compare volatile-based sedation (using AnaConDa) with IV sedation in patients who underwent elective cardiac surgery. Volatile-based sedation n=70 IV sedation (propofol) n=69	Use of volatile-based sedation resulted in shorter readiness/extubation time when compared to the IV group ($p<0.001$). Both groups had similar readiness/ discharge time from ICU. Volatile based-sedation offers a better sedation profile resulting in faster extubation time compared to short-acting IV propofol.
Wood (2021) Children requiring sedation on Paediatric Intensive Care Unit (PICU)	Retrospective UK case series Aim: to look at the relationship between the use of isoflurane via the AnaConDa for sedation on PICU, and iatrogenic withdrawal syndrome (IWS). Used in 22 admissions in n=20 patients	Duration of use (range): <24 hours to 19 days 59% showed signs of IWS IWS was observed consistently in children who were on isoflurane for >5 days Isoflurane can be used safely for prolonged sedation on PICU especially in children where enteral sedation is not possible.

Appendix D: Costs and Resources

Training costs included in the model

Parameter	Company value	Source	EAC value	Source	Comment
Training Sessions					
1 hour E-learning	N/A	N/A	£0	Company	Training is provided by the company at no cost.
Face to Face sessions (5 sessions, each 1 hour in length delivered over a 4-day period)	N/A	N/A	£0		Training is provided by the company at no cost.
Bedside support training	N/A	N/A	£0	Company	Training is provided by the company at no cost.
Total hours training	N/A	N/A	6 hours (with an additional 5 hours for an update training day)	Company	Based on the assumption that no additional training time is required for the bedside training element as this will be done during normal shifts.
Staff					
Consultant	N/A	N/A	2	Guidelines for the Provision of Intensive Care Services	Recommendation states that the Daytime consultant to patient ratio should not exceed a range between 1:8 and 1:12 and that most adult critical care units in the England and Wales have a bed capacity of between 9-16 beds.
Total cost for Consultant	N/A	N/A	£1,428	Based on £119 cost per hour for a hospital-based consultant (PSSRU 2020)	
Clinical Nurse Educator	N/A	N/A	1	Guidelines for the Provision of Intensive Care Services	
Total cost Clinical Nurse Educator	N/A	N/A	£360	Based on £60cost per hour for a hospital-based band 7 nurse (PSSRU 2020)	
Registered Nursing Staff	N/A	N/A	12	Guidelines for the Provision of Intensive Care Services	Based on the recommendation that level 3 patients should have a ratio minimum of 1:1 Median number of nursing staff required for a unit with 9-16 bed capacity

Parameter	Company value	Source	EAC value	Source	Comment
Total cost for registered nursing staff	N/A	N/A	£3,600	Based on £60cost per hour for a hospital-based band 7 nurse (PSSRU 2020)	
Senior Registered Nurse	N/A	N/A	2	Guidelines for the Provision of Intensive Care Services (2019)	1 supernumerary senior registered nurse for every 10 beds. Median number of beds in unit with 9-16 bed capacity is 12-13.
Total cost for Senior Registered Nurse	N/A	N/A	£828	Based on £60cost per hour for a hospital-based band 8a nurse (PSSRU 2020)	
Total training cost for an ICU team to deliver inhaled sedation using AnaConDa device	N/A	N/A	£6216		
Number of patients on inhaled sedation	100	Assumption	100		
Cost of training per patient	**N/A**	**N/A**	**£621.60**		

Appendix E: Changes to Comparison with Midazolam

Parameter	Value in Model	Source	EAC Value	Comment
Inhaled Isoflurane using AnaConDa				
Median duration of ICU stay (days)	8.5	Krannich 2017	No change	The EAC did not identify any alternative source
Median number of days on ventilator	7.1	Krannich 2017	No change	The EAC did not identify any alternative source
IV Midazolam				
Median duration of ICU stay (days)	13	Krannich 2017	No change	The EAC did not identify any alternative source
Number of days on Ventilator	11.2	Krannich 2017	No change	The EAC did not identify any alternative source
Cost of isoflurane with AnaConDa (including device and training costs)	£673.78		No Change	
Adult Cost of midazolam (including additional administration costs and daily sedation interruption)	£598.55		£1,120.70	Based on changes to average weight from 70kg to [redacted] and increased cost of nurse time for additional dosing and daily sedation interruption
Child cost of midazolam (including additional administration costs and daily sedation interruption)	N/A		£640.10 to £960.50	Based on changes to average weight from 70kg to 12kg, 24kg, 36kg, 48kg and 60kg to represent a range. As well as increased cost of nurse time for additional dosing and daily sedation interruption.

Parameter	Value in Model	Source	EAC Value	Comment
Adult Cost of ICU day (ventilated)	£1218	£1463	Weighted means for all 'organs supported'	
Adult Cost of ICU bed day (not ventilated)	£933	£914.82	Weighted means for all '0 organs supported'	
Child Cost of ICU	£0	£698.53	Weighted mean for all pediatric critical care	This cost has been used for both ventilated and non-ventilated days as there is no clear distinction between ventilated/non-ventilated for children in NHS reference costs.

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Addendum 1: Corrected Training Costs

Impact of Calculation Correction on Cost Savings

A calculation error in the cost of training has been corrected by the EAC. Training costs have been reduced to £62.16 per patient. The impact of this change has been to increase the cost savings associated with inhaled sedation using the AnaConDa device when compared with propofol.

Table 1: Propofol versus Isoflurane

Model	Cost of Intervention (Inhaled isoflurane using AnaConDa-S)	Cost of Comparator (IV Propofol)	Cost Saving
Company Base-case	£15,999.43	£19,647.73	£3,648.31
EAC Preferred Values	£18,703.83	£23,097.03	£4,393.20
Scenario 1: Days on ventilation are different for the sedation methods			
Company Scenario 1 (difference in ventilator days and ICU days between IV and inhaled sedation)	£15,507	£20,004	£4,497
Using EAC Preferred Values	£17,842.21	£23,797.63	£5,955.42
Scenario 2: ICU length of stay for total study population			
Company Scenario 2 (difference in ventilator days and ICU day in population including switchers)	£20,107.00	£21,141.66	£1,034.66
Using EAC Preferred Values	£23,166.41	£25,300.15	£2,133.74
Scenario 3: Sevoflurane for inhaled sedation			
EAC Additional Scenario: Sevoflurane for inhaled sedation with AnaConDa	£19,751.42	£23,097.03	£3,345.61

Similarly, the reduction in training costs results in increased cost savings with AnaConDa compared with Midazolam (table 2).

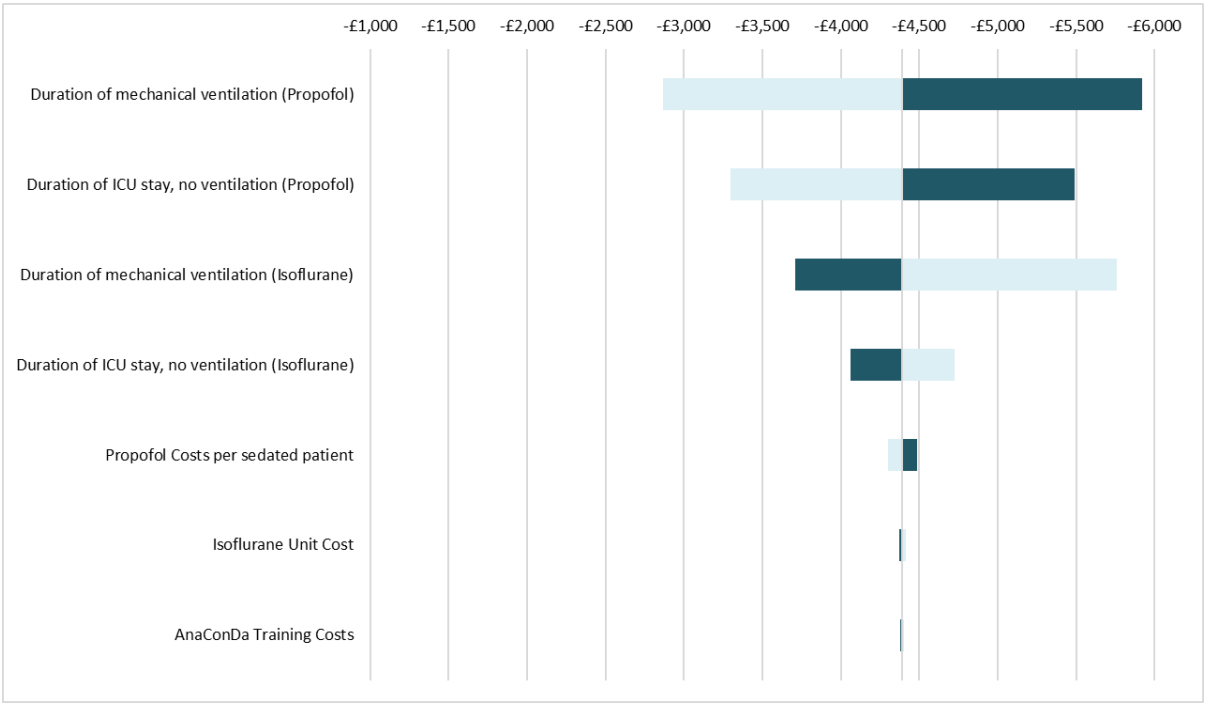
Table 2: Midazolam versus Isoflurane

Model	Cost of Intervention (Inhaled isoflurane using AnaConDa-S)	Cost of Comparator (IV Midazolam)	Cost Saving
Company Scenario	£10,161.28	£15,919.55	£5,758
EAC preferred inputs (Adult patients)	£12,508.88	£19,157.57	£6,648.69
EAC preferred inputs (Pediatric Patients)	£6,883.58	£9,720.99	£3,396.85

Sensitivity Analysis (AnaConDa vs Propofol)

Updated sensitivity analysis suggests that with the lower cost of training, AnaConDa remains cost saving even when duration of ICU stay is slightly longer with AnaConDa. This is because, with changes the EAC made to propofol costs (see Assessment Report) the cost of sedation with AnaConDa becomes marginally cheaper than with propofol per patient per day.

The EAC note that there is considerable uncertainty around the accuracy of the training costs and should be considered with caution.



		Duration of Additional ICU Stay													
		AnaConDa													
	-£4,393.20	18	17	16.5	16.3	15.5	15	14.5	14.2	13.5	13	12.5	12.4	11.5	10.5
Propofol	18	-£550.95	-£1,465.77	-£1,923.18	-£2,106.15	-£2,838.00	-£3,295.41	-£3,752.82	-£4,027.27	-£4,667.64	-£5,125.05	-£5,582.46	-£5,673.94	-£6,497.28	-£7,412.10
	17	£363.87	-£550.95	-£1,008.36	-£1,191.33	-£1,923.18	-£2,380.59	-£2,838.00	-£3,112.45	-£3,752.82	-£4,210.23	-£4,667.64	-£4,759.12	-£5,582.46	-£6,497.28
	16.5	£821.28	-£93.54	-£550.95	-£733.92	-£1,465.77	-£1,923.18	-£2,380.59	-£2,655.04	-£3,295.41	-£3,752.82	-£4,210.23	-£4,301.71	-£5,125.05	-£6,039.87
	16.3	£1,004.24	£89.42	-£367.99	-£550.95	-£1,282.81	-£1,740.22	-£2,197.63	-£2,472.07	-£3,112.45	-£3,569.86	-£4,027.27	-£4,118.75	-£4,942.09	-£5,856.91
	15.5	£1,736.10	£821.28	£363.87	£180.90	-£550.95	-£1,008.36	-£1,465.77	-£1,740.22	-£2,380.59	-£2,838.00	-£3,295.41	-£3,386.89	-£4,210.23	-£5,125.05
	15	£2,193.51	£1,278.69	£821.28	£638.31	-£93.54	-£550.95	-£1,008.36	-£1,282.81	-£1,923.18	-£2,380.59	-£2,838.00	-£2,929.48	-£3,752.82	-£4,667.64
	14.5	£2,650.92	£1,736.10	£1,278.69	£1,095.72	£363.87	-£93.54	-£550.95	-£825.40	-£1,465.77	-£1,923.18	-£2,380.59	-£2,472.07	-£3,295.41	-£4,210.23
	14.2	£2,925.36	£2,010.54	£1,553.13	£1,370.17	£638.31	£180.90	-£276.51	-£550.95	-£1,191.33	-£1,648.74	-£2,106.15	-£2,197.63	-£3,020.97	-£3,935.79
	13.5	£3,565.74	£2,650.92	£2,193.51	£2,010.54	£1,278.69	£821.28	£363.87	£89.42	-£550.95	-£1,008.36	-£1,465.77	-£1,557.25	-£2,380.59	-£3,295.41
	13	£4,023.15	£3,108.33	£2,650.92	£2,467.95	£1,736.10	£1,278.69	£821.28	£546.83	-£93.54	-£550.95	-£1,008.36	-£1,099.84	-£1,923.18	-£2,838.00
	12.5	£4,480.56	£3,565.74	£3,108.33	£2,925.36	£2,193.51	£1,736.10	£1,278.69	£1,004.24	£363.87	-£93.54	-£550.95	-£642.43	-£1,465.77	-£2,380.59
	12.4	£4,572.04	£3,657.22	£3,199.81	£3,016.85	£2,284.99	£1,827.58	£1,370.17	£1,095.72	£455.35	-£2.06	-£459.47	-£550.95	-£1,374.29	-£2,289.11
	11.5	£5,395.38	£4,480.56	£4,023.15	£3,840.18	£3,108.33	£2,650.92	£2,193.51	£1,919.06	£1,278.69	£821.28	£363.87	£272.39	-£550.95	-£1,465.77
	10.5	£6,310.20	£5,395.38	£4,937.97	£4,755.00	£4,023.15	£3,565.74	£3,108.33	£2,833.88	£2,193.51	£1,736.10	£1,278.69	£1,187.21	£363.87	-£550.95
		£15,915.81	£15,000.99	£14,543.58	£14,360.61	£13,628.76	£13,171.35	£12,713.94	£12,439.49	£11,799.12	£11,341.71	£10,884.30	£10,792.82	£9,969.48	£9,054.66

Addendum 2: Breakdown of costs and impact of removing daily sedation interruption and dose renewals

During the draft guidance meeting, the clinical experts requested a breakdown of the costs by sedation approach. This information is presented below – it should be noted that all results are based on a corrected cost of training.

Daily Sedation Interruption and Dose Renewals: These are included in the model for IV Sedation (Propofol) only.

The costs in the model are outlined in table 3.

Table 3: Cost by sedation approach

Sedation Approach	Cost per patient per day	Total cost for duration of sedation (10.9 days)
Propofol	£152.01 £43.34 is the cost of Propofol and £108.67 is the cost of the daily sedation interruption/dose renewal.	£1,656.94
Isoflurane	£95.76 £10.16 is the cost of isoflurane and £85.60 is the additional equipment costs for AnaConDa	£1,043.83

Based on the corrected training costs, if the daily sedation interruption and dose renewal costs are removed from the model, the cost savings associated with AnaConDa reduce from £4,393.20 to £3,208.71. This is for the base case, where the duration of ventilation is the same in both arms. In two-way sensitivity analysis (table 2), again with duration of ventilation equal in both arms, AnaConDa remains cost saving provided there is a reduction of 0.7 days overall ICU stay.

		Duration of Additional ICU Stay AnaConDa													
	-£3,208.71	18	17	16.5	16.3	15.5	15	14.5	14.2	13.5	13	12.5	12.4	11.5	10.5
Propofol	18	£633.54	-£281.28	-£738.69	-£921.66	-£1,653.51	-£2,110.92	-£2,568.33	-£2,842.78	-£3,483.15	-£3,940.56	-£4,397.97	-£4,489.45	-£5,312.79	-£6,227.61
	17	£1,548.36	£633.54	£176.13	-£6.84	-£738.69	-£1,196.10	-£1,653.51	-£1,927.96	-£2,568.33	-£3,025.74	-£3,483.15	-£3,574.63	-£4,397.97	-£5,312.79
	16.5	£2,005.77	£1,090.95	£633.54	£450.57	-£281.28	-£738.69	-£1,196.10	-£1,470.55	-£2,110.92	-£2,568.33	-£3,025.74	-£3,117.22	-£3,940.56	-£4,855.38
	16.3	£2,188.73	£1,273.91	£816.50	£633.54	-£98.32	-£555.73	-£1,013.14	-£1,287.58	-£1,927.96	-£2,385.37	-£2,842.78	-£2,934.26	-£3,757.60	-£4,672.42
	15.5	£2,920.59	£2,005.77	£1,548.36	£1,365.39	£633.54	£176.13	-£281.28	-£555.73	-£1,196.10	-£1,653.51	-£2,110.92	-£2,202.40	-£3,025.74	-£3,940.56
	15	£3,378.00	£2,463.18	£2,005.77	£1,822.80	£1,090.95	£633.54	£176.13	-£98.32	-£738.69	-£1,196.10	-£1,653.51	-£1,744.99	-£2,568.33	-£3,483.15
	14.5	£3,835.41	£2,920.59	£2,463.18	£2,280.21	£1,548.36	£1,090.95	£633.54	£359.09	-£281.28	-£738.69	-£1,196.10	-£1,287.58	-£2,110.92	-£3,025.74
	14.2	£4,109.85	£3,195.03	£2,737.62	£2,554.66	£1,822.80	£1,365.39	£907.98	£633.54	-£6.84	-£464.25	-£921.66	-£1,013.14	-£1,836.48	-£2,751.30
	13.5	£4,750.23	£3,835.41	£3,378.00	£3,195.03	£2,463.18	£2,005.77	£1,548.36	£1,273.91	£633.54	£176.13	-£281.28	-£372.76	-£1,196.10	-£2,110.92
	13	£5,207.64	£4,292.82	£3,835.41	£3,652.44	£2,920.59	£2,463.18	£2,005.77	£1,731.32	£1,090.95	£633.54	£176.13	£84.65	-£738.69	-£1,653.51
	12.5	£5,665.05	£4,750.23	£4,292.82	£4,109.85	£3,378.00	£2,920.59	£2,463.18	£2,188.73	£1,548.36	£1,090.95	£633.54	£542.06	-£281.28	-£1,196.10
	12.4	£5,756.53	£4,841.71	£4,384.30	£4,201.34	£3,469.48	£3,012.07	£2,554.66	£2,280.21	£1,639.84	£1,182.43	£725.02	£633.54	-£189.80	-£1,104.62
	11.5	£6,579.87	£5,665.05	£5,207.64	£5,024.67	£4,292.82	£3,835.41	£3,378.00	£3,103.55	£2,463.18	£2,005.77	£1,548.36	£1,456.88	£633.54	-£281.28
	10.5	£7,494.69	£6,579.87	£6,122.46	£5,939.49	£5,207.64	£4,750.23	£4,292.82	£4,018.37	£3,378.00	£2,920.59	£2,463.18	£2,371.70	£1,548.36	£633.54
		£17,100.30	£16,185.48	£15,728.07	£15,545.10	£14,813.25	£14,355.84	£13,898.43	£13,623.98	£12,983.61	£12,526.20	£12,068.79	£11,977.31	£11,153.97	£10,239.15

The impact of removing the daily sedation interruption and dose renewal costs on cost savings for each of the scenarios is outlined in table 4.

Table 4: Cost savings without daily sedation interruption and dose renewal for scenarios (based on corrected training costs)

Scenario	Company	EAC (with daily sedation interruption and dose renewal)	EAC (without daily sedation interruption and dose renewal)
Difference in ventilation days	£4,497	£5,955.42	£4,462.26
Mechanical ventilation and ICU duration for the whole population (switchers included)	£1,034.66	£2,133.74	£721.05
Sevoflurane	N/A	£3,345.61	£2,161.12

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

AnaConDa-S for sedation with volatile anaesthetics in intensive care

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

The Anaesthetic Conserving Device-S (AnaConDa-S; Sedana Medical) is a volatile anaesthetic delivery system to give isoflurane or sevoflurane to people who are invasively ventilated, usually in an intensive care setting.

AnaConDa-S is a single-use device (replaced every 24 hours or when needed). The device can be inserted into either the breathing circuit of a ventilator between the endotracheal tube and Y piece, replacing the heat and moisture exchanger (standard placement) or in the inspiratory port of the ventilator (alternative placement). Liquid anaesthetic is injected through the anaesthetic agent line, into a porous rod in the AnaConDa-S device where the anaesthetic is vaporised. The vaporised anaesthetic is then inhaled by the patient with the inspiration flow from the ventilator. With continued breathing, the majority of anaesthetic agent that has not been absorbed by the lungs is exhaled and adsorbed by an active carbon filter in the device. On further inhalation, the anaesthetic is desorbed from the filter and transported back to the lungs, reducing the amount of anaesthetic agent wasted. The AnaConDa-S device also contains a bacterial and viral filter and a gas analyser port. This port is used to measure the exhalated anaesthetic concentration in minimal alveolar concentration (MAC value; a relative measure of the level of anaesthesia) or end-tidal concentration (Fet%). Side stream or mainstream gas monitors, which can measure concentrations of carbon dioxide and anaesthetic gases, must be used to continually monitor anaesthesia, these will need to be purchased separately if not already available. AnaConDa-S is also recommended to be used with a gas scavenging system. This can be either via a passive system like the manufacturer's FlurAbsorb and FlurAbsorb-S products, or via an active scavenging system.

AnaConDa-S can be used with almost any kind of ventilator, except high-frequency ventilators. It was launched in the UK in 2017 and is a newer version of the AnaConDa device (available in the UK since 2005), which is now only available on request in the UK. The AnaConDa-S has a lower dead space of 50 ml (compared with 100 ml in the original device) and works with tidal volumes as low as 90ml. The lower dead space allows AnaConDa-S to be used on smaller adults or children who have smaller minute or tidal ventilation.

AnaConDa-S is a Class IIa medical device under MDD. The expiry date for the certification is 26/05/2024, but from 2023 products used in the UK will require a UK conformity assessment (UKCA). The manufacturer stated that they will have a designated Responsible Person in the UK from September 2021 to comply with the new rules and will apply for the UKCA nearer the 2023 deadline.

2 Proposed use of the technology

2.1 Disease or condition

Critically ill patients are frequently (>85% of patients) administered with sedatives to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm (Weinert et al., 2007; Jerath et al., 2017; Devlin et al., 2018). Sedation therefore can imply anything from anxiolysis (awake but very relaxed) to the induction of a state of unresponsiveness (Grounds, 2014). Sedation is not a substitute for analgesia and should not be prolonged beyond clinical need to avoid iatrogenic harm. Sedation in mechanically ventilated ICU patients is generally achieved by the IV infusion of propofol, midazolam or dexmedetomidine, in combination with opioids (Grounds, 2014; Devlin, 2018). Sedation is used to achieve a defined Richmond Agitation & Sedation Scale (RASS) score (with lower values implying deeper sedation) for each patient. In general, lighter sedation is preferred if possible (Devlin, 2018; Arora 2018), but clinical experts advised that this is not appropriate for all patients and can be difficult to achieve.

Optimal sedation helps patients to tolerate an endotracheal tube, allows for spontaneous breathing and minimizes iatrogenic harm.

2.2 Patient group

AnaConDa-S is intended to be used as an alternative to IV anaesthetics for sedating people who are mechanically ventilated in ICU. The AnaConDa-S has a tidal volume working range of 200 ml to 800 ml when used in standard placement. Small tidal volume (90 ml) can be achieved when AnaConDa-S is used in the alternative placement. Volatile anaesthetics should not be used in people with a known history of malignant hyperthermia. Using volatile anaesthetics in pregnant women, especially in the first trimester, could have potential teratogenic or developmental effects on the unborn baby. Clinical experts stated that any danger to the developing foetus would be weighed against the medical risk to the woman. As such, there is no absolute counterindication of the used of AnaConDa in pregnant women. The AnaConDa-S system could be used for people who need more rapid awakening for assessment; in people with difficult or limited IV access; or to manage sedation in cases when sedation is difficult despite using multiple sedative agents. Volatile anaesthetics can also be critical in treating severe acute asthma.

AnaConDa-S could be used in those with opioid dependence, in whom total withdrawal of opioids might not be desirable, CG52. The experts stated that they do not see any reason why the use of AnaConDa-S would be contraindicated in these patients.

2.3 Current management

Adults who need sedation in intensive care are sedated using IV sedatives and analgesics, primarily propofol or midazolam with alfentanil or morphine. Children in intensive care usually have sedation with IV midazolam and morphine or fentanyl.

The Intensive Care Society's 2014 review of best practice for analgesia and sedation in ICU (update to be published in 2021) states that there was insufficient evidence to recommend a particular sedation regimen and that the type of sedation should be individualised to the patient's requirements and situation. However, it also notes that the current evidence supports modest benefits in outcomes with non-benzodiazepine based sedation versus benzodiazepines.

The guideline also states that there are difficulties in delivering and scavenging volatile anaesthetics. There are also concerns about fluoride accumulation (with sevoflurane use) and the dependency of ventilation. Delivery devices, such as AnaConDa-S, as well as scavenging systems, make using isoflurane and sevoflurane in intensive care safer for staff. Isoflurane has shown safe, effective sedation for up to 96 hours in small studies, with faster awakening than midazolam. Isoflurane has shown improved awakening to propofol. Isoflurane is also a potent bronchodilator and is valuable in treatment for status asthmaticus.

AnaConDa-S is for use by healthcare professionals, trained to use inhalational anaesthetic drugs and recognise and manage any adverse effects, in an intensive care setting. In the NHS this would likely be intensivists and intensive care nurses. Usually sedation parameters (such as Fet% and MAC) would be set by an intensivist and modified if needed by nurses. Administration of isoflurane and sevoflurane using AnaConDa-S should only be done in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function.

The following publications have been identified as relevant to this care pathway:

- BNF treatment summary on anaesthesia (general).
- BNF for Children treatment summary on anaesthesia (general).
- Sedation for patients in ICU. Intensive Care Society Guideline.

- Medication concentration in critical care areas. Intensive Care Society Guideline
- British guideline on the management of asthma. British Thoracic Society and Scottish Intercollegiate Guidelines Network
- Guidelines on the Management of Acute Respiratory Distress Syndrome (ARDS). The Faculty of Intensive Care Society and Intensive care Society, supported by British Thoracic Society.

2.4 Proposed management with new technology

The intended place in therapy for AnaConDa-S would be as an alternative to IV sedation. It is expected to provide more flexible clinical management due to faster patient wake-up and cognitive recovery, which enables reduced time to extubation.

AnaConDa-S is already being used within the NHS. Some experts use it for sedating a variety of ICU patients while other clinicians only use it only in patients with bronchospasm. AnaConDa-S can be easily used within the sedation framework outlined by the Intensive Care Society (Grounds, 2014) as it allows for a variety of sedatives to be used and does not pre-specify the devices via which these sedatives should be delivered. As such, the EAC does not believe that there are any obstacles that would be prohibitive in the wider adoption of AnaConDa-S. Nevertheless, while common, the use of volatile sedatives in the ICU is an off-label use of these pharmacological agents (see correspondence log).

3 Company claimed benefits and the decision problem

These are described in the scope in Appendix C. The company did not propose any changes to the decision problem. The company did propose to treat AnaConDa-S and AnaConDa as the same intervention, highlighted where evidence is limited and that staff time would only be considered in the

economic analysis, while amount of sedative used and staff exposure would only be considered in the environmental impact assessment. The company noted that in the economic analysis they would only consider a comparison with standard intravenous (IV) sedation. The EAC noted that even though the company did not have any comments on the relevant subgroups, their search strategy excluded evidence from those under the age of 18 years. The company stated that current regulation does not cover pediatrics sedation with volatile agents in the intensive care setting, yet clinical experts noted that the regulation does not cover the use of volatile sedatives for adult patients in this setting either.

The EAC agreed with the company and made no changes to the decision problem. For further details please see section 1 in the EAC assessment report.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 25 full text studies (26 publications) from its literature search and one unpublished study (SED001). All 26 studies included, were used to inform the clinical evidence base. This comprised of 22 published comparative studies, 1 comparative unpublished study and 3 published retrospective comparative studies. Four systematic reviews were also identified by the company but the EAC decided not to use them to inform the clinical evidence because the primary studies were used instead.

The EAC undertook its own literature search (see section 4.1 of the EAC's assessment report). The EAC did not agree with the company's search strategies as they failed to include some key scope concepts. The EAC reran the searches to include key scope concepts. The EAC's revised search strategies are in Appendix A of the assessment report. The EAC identified 21 full text studies (reported in 23 publications). This comprised of 15 studies

submitted by the company, as well as 6 additional clinical studies (see Table 1 for details). The EAC excluded 9 of the studies included by the company (see Table 1 for details). The rationale for the selection and exclusion of these studies is in section 4.1 and 4.2 of the EAC assessment report. The EAC's search also identified 15 studies reported across 15 abstracts and included the 2 abstract only studies submitted by the company. Studies reported as abstracts were not included in the EAC's evidence review but details of the studies can be found in Appendix C of the EAC assessment report.

Table 1 summary of included studies

Studies included by both EAC and company	
Publication and study design	• 12 RCTs (Guerrero Orriach 2013; Hanafy 2005; Hellstrom 2012; Jabaudon 2017; Jerath 2015; Mesnil 2011; Rohm 2008 and 2009; Sackey 2004; SED001*; Soro 2012; Steurer 2012; Turktan 2019) • 1 prospective comparative study (Marcos-Vidal 2014) • 3 retrospective comparative study (Krannich 2017, Bellgardt 2016; Staudacher 2018)
Studies in submission excluded by EAC	
Publication and study design	In total, 9 studies were excluded by EAC. • 8 RTCs that used a different device to deliver volatile sedation (Bellgardt 2019, Daume 2021, Gomez 1995, Guinot 2020, Kong 1989, Meiser 2003, Millane 1992, Spencer 1992). • 1 RCT that reported on bispectral index (BIS) monitoring (Sackey 2007).
Studies not in submission included by EAC	
Publication and study design	6 additional studies were included by the EAC: • 2 comparative crossover studies (Marcos-Vidal 2020; Bomberg 2018) • 1 retrospective comparative study (Meiser 2018) • 1 comparative study using prospective intervention with a retrospective comparator (Jung 2020) • 1 retrospective comparative propensity score matched study (Foundraine 2021) • 1 RCT (Hellstrom 2011)
Abbreviations: EAC external assessment center; RCT randomized controlled trial Notes: * unpublished study	

All 21 included studies by EAC were comparative. Two studies compared the 2 versions of AnaConDa using a cross-over design (Bomberg 2018, Marcos-Vidal 2020). Thirteen studies were RCTs comparing volatile sedation using AnaConDa to IV sedation (Sackey 2004, Hanafy 2005, Rohm 2008 & 2009, Hellstrom 2011 & 2012, Mesnil 2011, Steurer 2012, Soro 2013, Guerrero Orriach 2013, Jerath 2015, Jabaudon 2017, Turktan 2019, SED001). Of the remaining 6 studies, 5 were retrospective studies (Krannich 2017, Bellgardt 2016, Meiser 2018, Staudacher 2018, Foundraine 2021), while 1 study collected data prospectively for the AnaConDa arm but utilized retrospective data for the IV arm (Jung 2020) and 1 was a prospective study (Marcos-Vidal 2014). All studies were conducted in adults and none of them were carried out in the UK.

Of the 21 studies comparing AnaConDa delivered sedation to IV sedation, 13 use sevoflurane (Mesnil 2011, Foundraine 2021, Rohm 2008 and 2009, Hellstrom 2011 and 2012, Steurer 2012, Soro 2012, Guerrero Orriach 2013, Marcos-Vidal 2014, Jung 2020, Jaboudone 2017 and Turktan 2019) and 7 use isoflurane as volatile anesthetic in the AnaConDa arm (Staudacher 2018, SED001, Sackey 2004, Hanafy 2005, Krannich 2017, Bellgardt 2016, Meiser 2018). Only 1 study used both isoflurane and sevolflurane delivered via AnaConDa (Jerath 2015). The comparative IV sedative agent was propofol in 12 studies (Staudacher 2018, SED001, Rohm 2008 and 2009, Hellstrom 2011 and 2012, Steurer 2012, Soro 2012, Guerrero Orriach 2013, Marcos-Vidal 2014, Jung 2020, Jerath 2015), midazolam in 4 studies (Jaboudone 2017, Sackey 2004, Hanafy 2005, Krannich 2017), both propofol and midazolam in 4 studies (Bellgardt 2016, Meiser 2018, Mesnil 2011 and Foundraine 2021) and dexmedetomidine in 1 study (Turktan 2019).

Six different type of populations were analysed in the 21 studies: post-cardiac surgery patients (Hanafy 2005, Rohm 2008, Hellstrom 2011 & 2012, Steurer 2012, Soro 2012, Guerrero Orriach 2013, Marcos-Vidal 2014, Jerath 2015), post-cardiac arrest patients receiving therapeutic temperature management (Krannich 2017, Staudacher 2018, Foundraine 2021), ARDS patients

(Jabaudon 2017, Meiser 2018), patients with various surgical indications (Rohm 2009, Bellgardt, 2016), head and neck surgery patients requiring tracheostomy (Jung 2020), patients with pulmonary disorders (Turktan 2019) and patients with over 12h (Sackey 2004) and 24h sedation requirements (Mesnil 2011, SED001).

The EAC did not include data from abstracts in its main report due to volume of evidence and potential overlap of study data, but details of these are reported in Appendix C of the EAC assessment report. Neither the company nor the EAC did a meta-analysis.

The EAC agreed with the company to consider AnaConDa-S equivalent to AnaConDa based on the results of 2 comparative cross-over trials (Marcos-Vidal 2020 and Bomberg 2018). See “Comparison of two AnaConDa versions” in section 5.3 of the EAC assessment report.

The EAC, following consultation with clinical experts, identified three outcomes of clinical significance: mechanical ventilation duration, wake-up time and sedation efficiency. Other outcomes reported across the trials were: ICU and hospital length of stay (LOS), cognitive and neurological results, cardiac, renal and hepatic markers and blood gas results.

Clinically significant outcomes

The EAC focussed on 8 comparative studies (4 RCTs, 2 retrospective cohort and 2 retrospective case-series studies) in their clinical evidence review (see Table 2 for details). The EAC judged 2 of the RCTs to have high risk of bias (Rohm 2008 and 2009), while the other 2 trials had some concerns with bias arising from the randomization process and bias due to deviations from intended interventions (Jerath 2015) and bias in measurement of the outcome (SED001). See Table 5 in section 5.2 of the EAC assessment report.

Of the other 2 comparative studies, 2 were deemed to be of medium quality (Staudacher 2018 and Bellgart 2016) and 2 were considered of high

methodological quality (Krannich 2017 and Meiser 2018). See Table 6 in section 5.2 of the EAC assessment report.

In terms of ventilation duration, a statistically significant difference between the volatile arm and IV arm was found in the matched analysis of Krannich 2017 comparing isoflurane and midazolam and in 2 RCTs (Rohm 2008 & 2009) comparing sevoflurane groups to the propofol groups in both studies. See details in Table 2 below and Table 7 of the EAC assessment report.

In terms of wake-up time (defined as time to extubation, the time from stopping the sedative infusion to taking out the endotracheal tube, or time to follow verbal commands) statistically significant differences between the volatile arm and IV arm was found in 4 RCTs trials (SED001, Rohm 2008 and 2009, Jerath 2015) for both isoflurane and sevoflurane versus IV propofol and in one retrospective comparative trial (Krannich 2017) which compared isoflurane versus IV midazolam. See details in Table 2 below and Table 7 of the EAC assessment report.

In terms of sedation efficiency (defined as isoflurane/sevoflurane consumption, opioid use, bispectral index [BIS] or time within desired sedation level) statistically significant differences between the volatile arm and IV arm were reported in the RCT SED001 trial [redacted] This trial also showed that sedation using isoflurane with AnaConDa was non-inferior to propofol in terms of maintaining adequate sedation without rescue sedation, [redacted] See details in Table 2 below and Table 8 of the EAC assessment report. Statistically significant improvements in sedation efficiency were also reported in a retrospective case series (Meiser 2018), in the isoflurane group at 6hrs and 24hrs and lower opioid use at 6 and 24h compared to the IV group (propofol, midazolam). In this trial, isoflurane patients also spent a significantly higher proportion of time breathing spontaneously while in deep sedation compared to the IV patients at 6h and at 24h. See details in Table 2 below

and Table 8 of the EAC assessment report. In studies comparing sevoflurane to propofol, no significant difference in sedation efficiency between the study arms was reported. See Table 8 of the EAC assessment report.

Other outcomes of interest

Sixteen studies reported on the ICU LOS, see Table 9 of the EAC assessment report. The ICU LOS was

[redacted]

Patients in the isoflurane arm had significantly shorter ICU LOS to midazolam in the matched pairs analysis of Krannich 2017 (see Table 2 below) and in the RCT Hannafy 2005 (see Table 4 of the EAC assessment report for a description of the trial and Table 5 of the EAC assessment report for a critical appraisal of the trial). The ICU LOS for patients treated with sevoflurane compared to IV midazolam or propofol was significantly shorter in only one comparative study Foundraine (2021). See Table 4 of the EAC assessment report for a description of the trial and Table 7 of the EAC assessment report for a critical appraisal of the trial.

Twelve studies reported on the hospital LOS, see Table 9 of the EAC assessment report. The hospital LOS was significantly shorter for the volatile arm in the observational study Foundraine (2021), which compared sevoflurane with both midazolam and propofol. The hospital LOS was also significantly shorter in both RCTs Rohm (2008 and 2009) for the sevoflurane group compared to propofol group. These results are important for the economic analysis and therefore additional detail has been added to Table 9 of the EAC assessment report.

Eight studies reported on cognitive/neurological outcomes, see Table 10 of the EAC assessment report. Statistically significant outcomes in favor of the

volatile arm were obtained in RCT Mesnil (2011) (see Table 4 of the EAC assessment report for a description of the trial and Table 5 of the EAC assessment report for a critical appraisal of the trial), which reported significantly better awakening quality in the sevoflurane group compared to the IV group ($p<0.001$) and in the observational study Foundraine (2021), which reported a significantly lower incidence of delirium in the sevoflurane group compared to the mixed IV group ($p=0.001$).

Nine studies reported on cardiac, renal and hepatic biochemical markers, please see Table 11 of the EAC assessment report. Among the sevoflurane treated arm, patients had significant lower cardiac troponin T in Steurer (2012) and Marcos-Vidal (2014), had significantly lower creatine kinase levels on postoperative day one in Steurer (2012), had significant lower levels of troponin I and N-terminal pro-brain natriuretic peptide in Guerrero Orriach (2013) when compared to patients in the propofol arm. Bellgardt (2016) reported significantly elevated C-reactive protein levels in the isoflurane group compared to the mixed IV group.

Six studies reported on patient blood gas results, see Table 12 of the EAC assessment report. Hellstrom (2011) reported a significant difference in central venous oxygen saturation at extubation with higher values in the sevoflurane arm. Steurer (2012) reported PaO_2/FiO_2 ratios to be better in the sevoflurane group compared to the propofol group on postoperative day 1 but no p value was given. Jabaudon (2017) reported significantly better PaO_2/FiO_2 ratios in the sevoflurane group compared to the midazolam group. Turktan (2019) reported significantly higher $PaCO_2$ levels at all time points except baseline in the sevoflurane arm compared to the dexmedetomidine arm.

The EAC noted several limitations that impact the quality, certainty and relevance of the available comparative evidence:

- There was a large clinical heterogeneity among the studies' populations and in the assessment of outcomes. This heterogeneity

reflects the ICU population and ICU clinical practice, but it affects trial inter-comparability.

- Comparative studies between volatile arms and IV arms were inconclusive in reference to all measured outcomes, excluding wake up times (usually reported as extubation time), which were reported better in the AnaConDa arm. All the included studies looked at different drug combinations and any differences between groups are likely to fundamentally be due to these drug differences as well as the variables involved in patient treatment and are unlikely to be solely attributed to the use of the device.

- No data on pediatric population were retrieved during the EAC literature search. The extrapolation of the efficacy of volatile sedation from adults to the pediatric population should take into consideration if it is reasonable to assume that children have a disease progression and response to intervention similar to adults.

See table 2 for full study details and outcomes of the comparative studies included in the EAC clinical evidence review for the 3 outcomes of clinical interest.

Adverse events

The EAC compiled a list of adverse events presented in the reviewed evidence base in Table 13 of the assessment report. There were no safety concerns relating to the use of the AnaConDa device because ICU patients are highly complex and as such the majority of adverse events are unlikely to be associated specifically to AnaConDa, but more likely due to the different medications to achieve sedation. The EAC reported that the clinical experts (see correspondence log) have acknowledged that the adverse events linked to the use of AnaConDa are likely to be similar to those linked to the use of heat and moisture exchanger.

Table 2 Summary of key comparative studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	EAC Comments
Rohm (2008) ***Design***: RCT **Location:** Germany **Setting:** ICU **Funding:** Hospital and department sources of the Klinikum Ludwigshafen, Germany. **Conflicts of Interest:** None reported	***Participants***: 70 cardiac patients were randomised into the two study arms Intervention n=35 Comparator n=35 **Patient demographics** **Intervention** • Mean age = 64.6 • Mean height= 171.7cm • Mean weight = 82kg • Male n=28 (80%) • **Comparator**: • Mean age = 66.4 years • Male n= 25 (71%) • Mean height= 169.5cm • Mean weight= 82kg	***Intervention***: AnaConDa + sevoflurane ***Comparator***: IV propofol	***Primary*** • extubation time ***Secondary*** • Sedation length • Ventilator time • ICU length of stay • Hospital length of stay • Adverse events • Bispectral index values ***Follow-up:*** Not reported	Median time to extubation (min) (IQR): • sevoflurane arm: 21.5 (8, 46) • propofol arm: 150.5 (69, 299) p<0.001 Mean ventilation time (hour) (SD) • sevoflurane arm: 9.0 (±4) • propofol arm: 12.5 (± 5.8) p= 0.0001 Mean sedation length (hour) (SD): • sevoflurane arm: 8.1 (± 3.1) • propofol arm: 8.4 (±4.2) p=0.87 Mean ICU length of stay (hour) (SD) • sevoflurane arm: 27.8 (± 14) • propofol arm: 39.6 (±35.5) p=0.062 Mean hospital length of stay (days) (SD) • sevoflurane arm: 10.6 (±3.3) • propofol arm: 14 (±7.7) p=0.026	Study outcomes differ from those stated in the trial registration information. Not UK/NHS setting No conflict of interest information was provided Some concerns in the overall risk of bias (in particular bias due to deviation from intended intervention)

Rohm (2009) ***Design***: RCT **Location:** Germany **Setting:** ICU **Funding:** None reported **Conflicts of Interest:** None reported	***Participants***: Initially 130 patients (1 patient in the sevoflurane arm and 2 in the propofol arm did not receive the allocated treatment and two propofol patients were lost to follow up. Intervention n=64 Comparator n = 61 **Patient demographics** Intervention: Mean age = 67 years Mean weight = 78kg Male = 72% Comparator: Mean age = 67 years Mean weight = 80kg Male n=44 (72%)	***Intervention***: AnaConDa + sevoflurane ***Comparator***: IV propofol	***Primary*** • Renal function parameters ***Secondary*** • Length of ICU and hospital stay • Sedation time • Sedative use • Time on ventilator • adverse events ***Follow-up:*** Not reported	Renal function Serum Creatinineand urine output remained unchanged and comparable with propofol-treated patients during the 48 hrs randomization. Mean sedation time (hour) (SD): • Sevoflurane arm: 9.2 (± 4.3) • Propofol arm: 9.3 (± 4.7) no p-value given Mean ICU length of stay (hour) (SD) • sevoflurane arm: 30.9 (± 20.7) • propofol arm: 38.8 (±45.9) no p-value given Mean hospital length of stay (days) (SD) • sevoflurane arm: 12.5 (±5.6) • propofol arm: 15.8 (±9.5) p<0.035 Mean ventilation time (hour) (SD) • sevoflurane arm: 10.2 (±4.5) • propofol arm: 13 (± 5.7) p< 0.009	Note this study had the same clinical trials registration number as Rohm (2008) above. Not UK/NHS setting. No conflict of interest and funding information was provided. Some concerns in the overall risk of bias (in particular bias due to deviation from intended intervention)

Jerath 2015 ***Design***: RCT **Location**: Canada and India **Setting**: Cardiovascular ICU **Funding:** States study was **not** funded by Sedana Medical **Conflicts of interest:** The authors declared conflicts of interest but none of these related to AnaConDa or Sedana Medical.	***Participants***: 141 patients undergoing coronary artery bypass graft (CABG) surgery with normal or mildly reduced left ventricular systolic function were randomised to either receive isoflurane or sevoflurane via AnaConDa or IV propofol Intervention n=67 Comparator n=74 **Patient demographics:** Intervention: Mean age =65 years Male n=61 (91%) Mean BMI= 28.3 Comparator: Mean age= 63 years Male n=70 (95%) Mean BMI= 29.9	***Intervention***: AnaConDa + sevoflurane or isoflurane ***Comparator***: IV propofol	***Primary*** • reduction in postoperative troponin level ***Secondary*** • Readiness to extubation time • Extubation time • Opioid consumption • Sedation score • ICU length of stay • Hospital length of stay ***Follow-up:*** Not reported	<u>Mean readiness to extubation time (min)</u> (range): • volatile arm: 135 (95-200) • Propofol arm: 215 (210-420) p<0.001 <u>Mean extubation time (min) (range):</u> • volatile arm: 182 (140-255) • propofol arm: 292 (210-420) p<0.001 <u>Mean hospital length of stay (days) (range):</u> • volatile arm: 6 (5-7) • propofol arm: 6 (5-8) p=0.79 <u>Mean readiness to ICU discharge time (min) range:</u> • volatile arm: 870 (490-1710) • propofol arm: 895 (670- 1485) p=0.22 <u>Mean ICU length of stay (min) (range)</u> • volatile arm: 1510 (1340-2990) • propofol arm: 1493 (1255- 2690) p= 0.34 <u>Cardiac markers</u> Cardiac index scores were significantly higher at ICU admission in the AnaConDa group compared to propofol (2.9 vs 2.5	Not UK setting Some concerns in the overall risk of bias (in particular bias due to randomization process and deviation from intended intervention)

				respectively, p<0.001). However, by ICU discharge, there was no significant difference between groups (2.5-2.6; p=0.55)	
Krannich (2017) ***Design***: retrospective matched cohort study **Location**: Germany **Setting:** ICU **Funding**: Not reported **Conflicts of interest:** Two authors declared conflicts of interests but none related to	***Participants***: 432 cardiac arrest survivors who underwent TTM. Intervention: n= 110 Comparator: n = 322 **Patient demographics for matched analysis (n=110 in both groups):** Intervention: Mean age= 62.3 years Male n=84 (76.4%) Comparator: Mean age =61.9 years Male n=81 (73.6%)	***Intervention***: AnaConDa + isoflurane ***Comparator***: IV sedation using combination of Midazolam and fentanyl	• Time on ventilator • Length of ICU stay • Neurological outcomes • NSE serum concentration • Adverse events ***Follow-up:*** Not reported	Median ventilation time (hour) (IQR) in the overall group analysis • Isoflurane arm: 170 (87-323) • Midazolam arm: 210 (99-450) p=0.068 Median Ventilation time (hour) (IQR) in the matched pair analysis: • Isoflurane arm: 170.5 (87.5-323.5) • Midazolam: 269 (122.2-530.2) p=0.003 Median ICU length of stay (days) (IQR) in the overall group analysis: • sevoflurane arm: 8 4-16) • propofol arm: 11 (4-23) p= 0.116 Median ICU length of stay (days) (IQR) in the matched pair analysis: • sevoflurane arm: 8.5 (4.2-16) • propofol arm: 13 (6-26.7) p= 0.006	Retrospective design Not NHS setting Midazolam is not the sedative of choice in the UK for the adult population. Patient demographics not reported for sample a whole. No funding information was provided High quality observational study

Sedana Medical. Please see page 55 of the EAC assessment report for further information.					
Bellgardt (2016) ***Design***: retrospective cohort study **Location**: Germany **Setting**: ICU **Funding:** None reported **Conflicts of Interest:** None reported	***Participants***: 200 patients in the final study population from an initial cohort of 369 patients, with 46 patients excluded due to mixed sedation, 103 fell outside the age criteria and 20 were lost to follow-up Intervention: n= 72 Comparator: n = 128 ***Patient demographics*** Intervention Male = 46%	***Intervention***: AnaConDa + isoflurane ***Comparator***: IV propofol or midazolam	***Primary*** in-hospital mortality ***Secondary*** 365 day mortality after first admission to ICU ***Other outcomes:*** • Invasive ventilation length • Ventilator free days at 30 and 60 days • Lengths of ICU and hospital stay as well as hospital-free days at 90 and 180 days • Laboratory results • ICU admissions	Mortality (%) • Isoflurane arm: 29 (n=40) • IV arm: 81 (n=63) p=0.005 365-day Mortality (%) • Isoflurane arm: 36 (n=50) • IV arm: 89 (n=70) p=0.013 Mean ventilation length (hour) (SD): • Isoflurane arm: 506 (± 354) • IV arm: 431 (±377) p=0.17 Mean ventilator-free days (days) at 30 days • Isoflurane arm: 7.4 (±9.5) • IV arm: 7.7 (±10.4) p=0.81 Mean ventilator-free days (days) at 60 days	Retrospective/non-randomised study character. IV arm is mixed propofol and midazolam. Midazolam is not the sedative of choice in the UK for the adult population. The study also reported some outcomes for patients who received mixed sedation. The study reports a comprehensive list of complications but due to lack of detail it was not possible to classify them according to the Clavien-Dindo system. There was no statistically

	Mean age = 66.4 years Comparator Male = 38% Mean age = 67.7 years		• Complication (pneumonia, peritonitis, sepsis, thrombosis/embolism, stroke, acute renal failure, mass bleeding) ***Follow-up:*** 365 days	• Isoflurane arm: 32.5 (±29.2) • IV arm: 23.2 (±28.2) p=0.03 <u>Mean ICU length of stay (days) (SD)</u> • isoflurane arm: 30 (± 20) • IV arm: 26 (±20) p=0.19 <u>Mean in-hospital length of stay (days) (SD)</u> • isoflurane arm: 60 (± 39) • IV arm: 48 (±39) p=0.08 <u>Mean hospital-free days at 90 days (days) (SD)</u> • isoflurane arm: 14.7 (± 22.2) • IV arm: 13.7 (±13.4) p=0.77 <u>Mean hospital-free days at 180 days (days) (SD)</u> • isoflurane arm: 62.1 (± 59.5) • IV arm: 44.1 (±64.8) p=0.04	significant difference in the frequency of these complications between both groups. Not UK setting Medium quality observational study
Meiser (2018) ***Design***: retrospective	***Participants***: 38 patients were included in the study. Intervention n = 19	***Intervention***: AnaConDa + isoflurane	• Sedative use • Ventilation parameters/ pulmonary mechanics	<u>Mean ICU length of stay (days) (SD)</u> • isoflurane arm: 30 (± 14) • IV arm: 36 (±33) p=0.48 <u>Mean in-hospital length of stay (days) (SD)</u>	Isoflurane sedation was available from June 2011.

case series analysis **Location**: Germany **Setting**: ICU **Funding:** None reported **Conflicts of Interest:** Meiser declared a relationship with Sedana Medical and Pall Medical. No other conflicts were declared	Comparator n = 19 Patient demographics Intervention: Male= 74% Mean age= 48.9 years Mean BMI = 28.3 Comparator: Male = 63% Mean age = 56.3 years Mean BMI = 25.0	***Comparator***: IV propofol or midazolam	• Blood gases • RASS score • Cardiovascular parameters • Length of invasive ventilation • Length of patient stay • Mortality during continuous lateral rotational therapy ***Follow-up:*** Not reported	• isoflurane arm: 45 (± 27) • IV arm: 51 (±37) p=0.60 <u>Mean of invasive ventilation (hour) (SD)</u> • isoflurane arm: 465 (± 230) • IV arm: 618 (± 503) p=0.26 <u>Mortality during continuous lateral rotational therapy (n) (%)</u> • isoflurane arm: 2 (11) • IV arm: 4 (21) p=0.39 <u>RASS score at 6h and 24 h</u> Isoflurane sedated patients had significantly deeper sedation than IV arm patients at 6h and 24h post after initiation of continuous lateral rotational therapy (p=0.03 and p<0.001 respectively). <u>Opioid use</u> In the isoflurane arm, opioid use was lower at 6h and 24h compared to the IV arm (p<0.001 and p<0.001 respectively). <u>Spontaneous breathing at 6h (n) (%)</u> • isoflurane arm: 12 (63) • IV arm: 3 (16) p=0.003	Midazolam is not the sedative of choice in the UK for the adult population. The manuscript does not state the dose range used for IV sedatives, nor does it state whether the same criteria were used to target sedation depth. Evidence limited to patients undergoing continuous lateral rotational therapy. Not UK/NHS setting. No funding information was provided Medium quality observational study

				Spontaneous breathing at 24h (n) (%) • isoflurane arm: 17 (90) • IV arm: 3 (16) P<0.001	
Staudacher (2018) ***Design***: retrospective case series analysis **Location**: Germany **Setting**: ICU **Funding:** None reported **Conflicts of Interest:** None reported	***Participants***: 214 patients were included in the study Intervention n = 36 Comparator n = 178 **Patient demographics** Isoflurane: Median age= 66.6 years Male = 86.1% BMI = 27.1 Comparator: Median age= 66.0 years Male = 68.0% BMI = 25.5 Additional analysis was carried out on propensity score matched patients (36 from each arm).	***Intervention***: AnaConDa + isoflurane ***Comparator***: IV propofol	• Patient survival • Delirium • Mechanical ventilation length • ICU stay • Hospital stay • Time to spontaneous breathing ***Follow-up:*** Not reported	Median mechanical ventilation (hour) and IQR in the overall group analysis: • Isoflurane arm: 99.0 (65.3–115.7) • Propofol arm: 105.7 (93.3–118.1) p=0.692 Median mechanical ventilation (hour) and IQR in the matched cohort analysis: • Isoflurane arm: 99.0 (65.3–115.7) • Propofol arm: 93.1 (59.1–143.3) p=0.426 Median ICU length of stay (days) (IQR) • isoflurane arm: 11.1 (8.6-13.5) • propofol arm: 9.8 (8.9-10.8) p=0.320 Median hospital length of stay (days) (IQR) • isoflurane arm: 15.1 (11.4-18.9) • propofol arm: 13.1 (11.9-14.3) p=0.218 Median time to first spontaneous breathing (hour) (IQR) • isoflurane arm: 9.3 (2.5-24.8)	Significant difference (p=0.028) in patient sex between both arms. Retrospective/non-randomised study. Higher proportion of male patients in the isoflurane group. Propofol arm included patients from 2014-2017, while isoflurane arm included patients from 2015-2017. For some parameters two different analysis were carried out (e.g. Fisher's exact test and Mantel-Cox test). Not UK/NHS setting.

				• propofol arm: 9.5 (8.9-10.8) p=0.320 Hospital survival: Total hospital survival: 69.6% Delirium (%) • isoflurane arm: 41.7 (n=15) • IV arm: 35.4 (n=63) p=0.569	Funding information was not provided. Medium quality observational study
SED001 ***Design***: RCT, non-inferiority study **Location:** Germany and Slovenia **Setting**: ICU [redacted]	***Participants***: [redacted]	***Intervention***: AnaConDa + isoflurane ***Comparator***: IV propofol	***Primary*** • Maintenance of adequate sedation ***Secondary*** [redacted] ***Follow-up:*** 30 days	Maintenance of adequate sedation: [redacted] Wake up time [redacted] Spontaneous breathing [redacted] Opioid use: [redacted] Mean ICU length of stay(days) whole study population [redacted]	[redacted] Some concerns in the overall risk of bias (in particular bias in the measurement of outcome)

				[redacted] Mean ICU length of stay(days) [redacted] [redacted] Mean mechanical ventilation (days[redacted] Mean mechanical ventilation (days[redacted]	

Abbreviation: IQR= interquartile range; SD= Standard deviation

*

Conclusions on the clinical evidence

A crucial factor in evaluating the effectiveness of AnaConDa-S is that inhaled sedation uses different sedative agents from the standard of care IV sedation. The EAC focused their assessment report on the evidence around the use of AnaConDa-S device only, excluding any comparison between different sedative agents or stating whether either inhaled or IV sedation is preferable.

The type of sedative agents, as highlighted by clinical experts and general guidelines on the use of sedation within the ICU, is a clinical decision based on patient's requirements and situation.

The EAC concluded that the use of AnaConDa-S delivered sedation was consistently associated with faster wake-up time and faster extubation time, but not in reductions of ICU LOS or hospital stay. However, the EAC noted that for long term outcomes (ICU LOS, hospital stay) the type of sedation received will only be one of several factors potentially affecting that outcome because the patient population in ICU is complex, often including polypharmacy and various technological interventions supporting patients' organ systems (see page 26-27 of the EAC correspondence log for expert advice highlighting the presence of confounders).

Overall, the EAC stated that even differences in outcomes that are highly dependent on sedation time (like wake-up time and extubation time) are likely to be due to the type of sedative agent used and not to the use of the AnaConDa-S device itself. The EAC did not find any comparative studies between AnaConDa-S and similar competitor devices.

The EAC reported that when Anaconda-S is used with a scavenging system (Pickworth 2013, Bos 2017, Sackey 2005, Herzog-Niescery 2018; see section 8.1 of the EAC assessment report) the environmental exposure of isoflurane to workers is below 2 ppm and less than 10 ppm when the ventilatory circuit is opened. These concentrations are likely to comply with UK staff exposure regulations (Health and Safety regulations (EH40/2005). The EAC also noted that there is uncertainty about whether the use of the AnaConDa would be

associated with a lower consumption of volatile sedatives compared to other standard vaporisers as there were no recent data available.

4.2 Summary of economic evidence

The EAC noted that the company's search strategy for the economics was broad and not focused on the key concepts of the scope. The company included 2 published studies in its submission (Sackey 2018, L'Her 2008). According to the EAC, these studies were somewhat relevant but were not considered to be of adequate quality to undergo formal critical appraisal (see section 9.1 of the EAC assessment report). These publications were very limited in reporting clinical, cost and resource data and it was not possibile to validate the results, hence they were excluded. See Table 16 and Table 17 in section 9.1 of the EAC assessment report. The EAC's search did not identify further economic studies on AnaConDa-S.

De novo analysis

The company submitted two cost analyses using two cost comparison models comparing inhaled sedation using the AnaConDa-S device with IV sedation. One model compared inhaled isoflurane with IV propofol and the other model compared inhaled isoflurane with IV midazolam. Both cost models had a 30-day time horizon and included adult patients requiring mechanical ventilation for ≥24 hours in ICU. Both cost models were based on an NHS and personal social services perspective and no discounting was applied as the time horizon of the models was less than 1 year. See Figure 3 of the EAC assessment report for a description of the company's cost model structure.

The EAC focused on the inhaled isoflurane delivered by AnaConDa-S versus IV propofol model as it reflected clinical practice in the NHS. The other model was used to carry out an additional analysis exploring the use of inhaled sedation in children. More details on this analysis will be given in the additional results section below.

The company model made a few assumptions which are discussed in Table 18 in section 9.2 of the EAC assessment report. Overall, the EAC considered the assumptions made by the company were appropriate for the modelled scenario as they reflected clinical practice in the NHS:

- Isoflurane is the most common sedative agent used in inhaled sedation
- IV propofol is the most common drug for sedation in adults
- IV sedation required more frequent dose renewal and daily dose interruption
- Sedation efficacy, tolerability and safety do not differ by sedation strategy (Inhaled isoflurane using AnaConDa versus IV sedation)
- There are differences in sedation costs, monitoring and administration by sedation strategy

The EAC identified additional assumptions in the model:

- The model assumes that the mean body weight of an adult in the UK is 70 kg, but the company did not provide the source of this value. The EAC used the mean body weight calculated from the trial SED001, which was [redacted] kg.
- The model assumes that there is a cost for purchasing a mixed gas analyser associated with the use of AnaConDa-S. The EAC noted that not all ICUs will incur this cost as some may already have a suitable analyser. However, The EAC has not removed this cost noting it is potentially a conservative assumption.
- The model includes 180 days of use of a gas analyser per year with replacement every 5 years. The EAC noted that no source for the estimate of the gas analyser usage was provided, however the EAC estimated that the cost of the analyser would not impact the cost-saving.

- The model does not include any training cost associated with the switch between IV sedation to inhaled sedation. The EAC included an initial cost for training ICU staff and assumed that new staff joining the ICU unit will receive inhaled sedation training as part of their routine training. The training cost is associated with staff time spent on training as the company offers training on AnaConDa-S free of charge and it is spread across an assumption of 100 patients being sedated using AnaConDa-S.

See Table 18 of the EAC assessment report for a full list of the model assumptions.

Model parameters

The clinical input parameters used in the company's model include the mean body weight of people sedated in ICU, the duration of mechanical ventilation (mean in days) and the ICU LOS (mean in days). These parameters were sourced from the unpublished trial SED001. The duration of mechanical ventilation and the ICU LOS were calculated from a subset [redacted] of the trial population ([redacted], namely only from sedated people [redacted]. The use of this subset of data prompted the EAC to state that the certainty of the values of duration of mechanical ventilation and ICU LOS should be treated with caution.

In the base-case analysis, the company modelled a scenario where there was no significant difference in mean number of days spent on mechanical ventilation [redacted] but significant difference in mean ICU LOS between AnaConDa arm [redacted] and IV propofol [redacted]. The EAC agreed with the data source used for the clinical parameters but made a change in the value of the mean body weight in the model, from 70 kg to [redacted] kg, based on data from the SED001 trial.

A full description of the clinical parameters is outlined in Table 19 in section 10.2.3 of the EAC assessment report.

Costs and resource use

The cost and resource use parameters for inhaled sedation with AnaConDa-S in the company model included costs of inhaled drug, costs of the AnaConDa-S device and necessary accessories such as filters and multi-gas analyzers. Healthcare resource utilization costs for IV sedation included costs of sedative drug, costs for infusion syringes, cost of nurse time required for syringe changes and cost for daily sedation interruption (DSI). Other resource utilisation costs included in the model were costs of ICU bed day with/without ventilation.

The EAC agreed with the healthcare resource use identified by the company but made some changes. Moreover, the EAC identified 2 additional parameters to be included in the inhaled sedation arm of the model: training time for ICU staff and the number of ICU staff included in the training.

The key changes that the EAC made to the company model were:

- Cost of propofol sedation per person: the EAC used the BNF as the source of propofol unit cost and propofol dose. The EAC total cost per person for propofol (£472.45) was higher than the company cost (£228.53) as it was based on a higher propofol unit cost. This change increased the cost savings compared to the company model.

- Additional IV sedative costs: the EAC used the hourly overhead cost of 2 band 6 hospital-based nurses (£50 per hour), sourced from the PSSRU 2020, to calculate the cost of nurse time required for syringe changes and cost for daily sedation interruption (£1184.5). The additional IV sedative costs from the company model was £545.87, this was based on staff time costed at £20 per hour. This change increased the cost saving.

- Cost of training required when switching from IV sedation to inhaled sedation: the EAC estimated that there was a cost associated with the time staff spent on training (£621.60), although company provides training to staff free of charge. See appendix D in the EAC assessment report for more details. This change increased the cost saving.

- Costs of ICU bed day with/without ventilation: the EAC calculated the cost of ICU bed day using a weighted mean of all HRG codes for adult critical care except "0" code (organs supported) from the NHS reference cost 2018-19 instead of using a mean unit cost for critical care from NHS reference cost 2018-19 as the company did. The costs were similar between company and EAC value, this change has not had a major impact on the cost saving.

See Table 20 of the EAC assessment report for full details of the cost and resource use parameters used in the company and EAC base case model.

Results

Both the company and the EAC estimated cost savings from the use of AnaConDa-S in adult patients requiring mechanical ventilation for ≥24 hours in ICU. The company and the EAC base case results, £3,648.31 and £3,833.76 respectively, are presented in Table 3 below.

Table 3. Company and EAC base case results (SED001)

Cost category per patient	Company's base-case			EAC's base-case		
	Device	Comparator	Cost saving per patient*	Device	Comparator	Cost saving per patient*
Sedation	[redacted]	£228.53	[redacted]	[redacted]	£472.45	[redacted]
Additional cost for IV sedation	£0	£545.88	-£545.88	£0	£1184.49	-£1184.49

Device costs	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
Training	£0	£0	£0	£621.60	£0	£621.60
ICU bed day with ventilation	£13,276.2	£13,276.2	£0	£15,591.17	£15,591.17	£0
ICU bed day without ventilation	£1,568.62	£5,598	-£4,029.38	£2,255.79	£5,849.09	-3,593.3
Total	**£15,999.43**	**£19,648.61**	**-£3,648.31**	**£19,263.27**	**£23,097.03**	**-£3,833.76**
** A minus sign indicates cost saving.*						

Sensitivity analysis

The company's one-way deterministic sensitivity analysis (DSA), which varied each base case parameter by ± 20%, found inhaled isoflurane using AnaConDa-S remain cost saving in all cases. This result was confirmed by the EAC after changing the company values to EAC preferred inputs.

The key driver for cost saving was the mean duration of mechanical ventilation (Figure 4 in section 9.3 of the EAC's assessment report). The shorter the time a patient spend under mechanical ventilation, the greater the cost saving will be, this is mainly because of reduced time spent in an ICU unit. However, the company threshold analysis showed that if the duration of mechanical ventilation was the same in both arms, inhaled isoflurane using AnaConDa-S would be at least cost neutral when the duration of non-ventilated ICU days was 0.33 days lower than that of IV propofol. The EAC threshold analysis, using their preferred inputs confirmed inhaled isoflurane using AnaConDa-S would be cost saving compared to IV propofol when the duration of non-ventilated ICU days was in the region of 0.1-0.2 days and the duration of mechanical ventilation was the same (refer to Figure 5 of the EAC's assessment report).

The EAC 2-way sensitivity analysis found inhaled sedation delivered using AnaConDa-S remained cost saving for all comparisons when varying the unit

costs of propofol and isoflurane (Figure 6 of the EAC's assessment report). Cost saving ranged from around £3,331.14 when unit cost of isoflurane was the highest to £4,842 when unit cost of propofol was the highest.

Scenario analysis

The company submitted 2 scenario analyses (scenario 1 and 2) and 1 additional scenario analysis (scenario 3) was carried out by the EAC (see Table 22 of the EAC's assessment report).

In scenario 1 the company assessed the impact of different duration of mechanical ventilation for inhaled isoflurane delivered via AnaConDa-S [redacted] and IV propofol [redacted]. Data on duration of mechanical ventilation were sourced from the population of "non-switchers" in the SED001 trial. The cost saving associated with inhaled sedation using AnaConDa-S increased to £4,497 per patient from £3,648.31 in the base case. The cost saving rose to £5,395.98 when using the EAC preferred values as inputs for all other parameters.

In scenario 2 the company examined the impact of using data about duration of mechanical ventilation and ICU LOS from the whole study population in SED001 trial

[redacted]. This scenario was still cost saving for inhaled isoflurane using AnaConDa-S compared with IV propofol of £1,034.66 per patient. The cost saving reached £1,574.30 when the EAC preferred values for all other inputs were used.

In scenario 3 the EAC explored the impact of using inhaled sevoflurane as an alternative to inhaled isoflurane delivered via AnaConDa-S. The cost saving of inhaled sevoflurane versus IV propofol was £2,657.08 per person.

Additional results

The EAC used the second model submitted by the company to explore the economic impact of using inhaled sedation in children. In this model the

comparator was IV midazolam and clinical parameters (ICU LOS, duration of mechanical ventilation, body weight) were informed from Krannich 2017. See Appendix E in the EAC assessment report for a list of EAC adaptations from the company model. The company base case result showed a cost-saving of £5,758 per adult patient (see Table 23 of the EAC assessment report). Using the EAC preferred inputs, the cost saving increased to £6,648.69 per adult patient.

In children, the EAC adapted model estimated a cost saving of £2,837.41 per child. However, the EAC stated that the result of this modelling should be treated with extreme caution. This is because the duration of ICU stays and days on mechanical ventilation, which were sourced from an adult population in Krannich 2017, may be very different for pediatric patients and this would likely have a significant impact on cost savings. The EAC also suggested that cost of pediatric ICU for children and training to deliver inhaled sedation for pediatric patients might be very different than for adult patients. See section 9.3 of EAC assessment report (additional results).

Conclusions on the economic evidence

In general, the EAC agreed with the model submitted by the company and made only changes in input parameter values that resulted in favourable changes for inhaled sedation using AnaConDa-S.

The economic results showed that delivering inhaled sedation with isoflurane using the AnaConDa-S device is cost saving compared to IV sedation with propofol. However, the EAC cautioned that the key clinical parameters driving the cost-saving were uncertain because were sourced from a subgroup analysis (non-switchers) in SED001 trial. The SED001 trial was not powered to estimate difference in either ICU LOS or duration of mechanical ventilation from a subgroup analysis.

5 Sensitivity analysis indicated that the model was robust to changes to drug doses, drug

costs and to the addition of training costs with AnaConDa-S.

Ongoing research

The company did not identify any ongoing studies in their submission. The EAC identified 4 ongoing and 2 completed studies (not peer-reviewed or published). Details of these studies can be found in table 15 of the EAC assessment report (page 106). Notably, NCT04684238 is a paediatric study.

6 Issues for consideration by the Committee

Clinical evidence

- AnaConDa-S delivered sedation offers benefit over IV sedation in terms of extubation time and wake-up time, but this is likely attributed to the volatile sedatives that AnaConDa-S allows to administer.

- None of the studies provided evidence on any of the pre-specified subgroups, though some experts only use the device in the context of treating patients with bronchospasm due to the properties of the volatile sedatives rather than those of the device. The committee should consider whether is it appropriate to recommend volatile anaesthetic for sedation in any particular patient group or whether the choice should be left to clinicians.

- The use of volatile sedatives in the ICU is an off-label use of these pharmacological agents. Nevertheless, AnaConDa is already used in the UK ICU setting and off-label use of therapies is common in the paediatric setting. Based on the reported adverse incidents, AnaConDa-S does not present a risk that is outside of the normal range relating to the use of ICU equipment.

- The interpretation of the evidence from the SED001 trial report presents several difficulties due to how certain outcomes were

presented. The duration of mechanical ventilation was presented [redacted] not as the actual amount of days patients spend on mechanical ventilation and the ICU LOS was presented [redacted] and not the actual amount of days patients spend on ICU. The EAC understood that ICU LOS and duration of mechanical ventilation [redacted] As such, the results of this trial should be treated with caution.

- The committee should also consider if volatile sedation delivered via AnaConDa is clinically better than other ways of delivering volatile sedation in ICU.

Cost evidence

- No useful published economic studies were identified

- The key driver for the cost savings is the duration of ICU stay, including the duration of mechanical ventilation. The EAC noted that the limitations of the ICU length of stay and duration of ventilation data in the cost analysis is that it is taken from a subset of patients in a clinical trial (SED001) and is therefore not powered for this outcome.

- The committee should consider if volatile sedation delivered via AnaConDa is economically better than other ways of delivering volatile sedation in ICU.
- No clinical evidence for inhaled sedation with AnaConDa in children. There is uncertainty around the cost of ICU days/ventilator days for children and duration of ICU stays and days on ventilation may be very different for pediatric patients (data from Krannich 2017 may not be generalisable). The cost of pediatric ICU and training to deliver inhaled sedation for pediatric patients might be very different than for adult patients.

7 Authors

Federica Ciamponi, health technology assessment (HTA) analyst

Kimberley Carter, HTA adviser

NICE Medical Technologies Evaluation Programme, July 2021

Appendix A: Sources of evidence considered in the preparation of the overview

Details of assessment report:

- Pruski M, O'Connell S, Knight L, et al. AnaConDa-S for sedation with volatile anaesthetics in intensive care, July 2021.

Submissions from the following sponsors:

- Sedana Medical AB (publ)

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Jonathan Ball

Consultant in Critical Care Medicine, St George's University Hospitals NHS Foundation Trust.

Mark Blunt

Consultant in Critical Care Medicine, Queen Elizabeth Hospital King's Lynn

Stephen Playfor

Consultant in Pediatric Intensive Care, Manchester University NHS Foundation Trust

Professor Anil Hormis

Consultant in Anesthesia and Intensive Care Medicine, Rotherham NHS Foundation Trust.

Guy Glover

Consultant in Critical Care and Anesthesia, Guy's and St Thomas' NHS Foundation Trust

Paul Dean

Consultant in Critical Care and Anesthesia, Guy's and St Thomas' NHS Foundation Trust

Tom Syrat

Cheshire and Mersey Critical Care Network

Please see responses to the expert advisor questionnaire (EAQ) included in the committee pack for full details.

Appendix C: Decision problem from scope

Population	People who are invasively ventilated in intensive care using a mechanical ventilator but not a high frequency ventilator.
Intervention	AnaConDa-S AnaConDa (previous version)
Comparator(s)	IV sedatives Standard vaporiser
Outcomes	The outcome measures to consider include: • wake-up time after ICU sedation • cognitive recovery • sedation efficacy (time to extubating, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale) • markers of cardiac injury, liver, gut, kidneys and brain for short-term operative sedation • sedation effectiveness in patients with life-threatening bronchospasm and asthma • oxygenation and inflammatory markers in patients with ARDS • psychological outcomes (e.g. memories of hallucination, and long-term psychological morbidity, PTSD) • Effectiveness of ventilation on people with bronchoconstriction • Reduction of additional bronchodilators • duration of mechanical ventilation/ increased ventilator-free days • length of stay in the ICU. • hospital length of stay/ hospital-free days. • Amount of volatile anaesthetic agent used • Staff exposure to volatile anaesthetic agents • Staff time in the ICU • Amount of opioid drug used • Device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	People with acute asthma that need to be mechanically ventilated.

	People with acute respiratory distress syndrome that need to be mechanically ventilated Children that need to be mechanically ventilated Patients who need to have regular neurological wake up tests performed. People who are intolerant to IV sedation (e.g people who misuse alcohol, people who misuse drugs, people on overdose, people with COVID-19) People with hepatic and renal failure People with super-refractory status epilepticus People under prolonged sedation who need an IV sedation break (due to being at risk of developing tolerance, tachyphylaxis and/or propofol infusion syndrome)	
Special considerations, including those related to equality	Volatile anaesthetics may not be suitable for pregnant women. Volatile anaesthesia may particularly benefit children for whom sedation is difficult. Volatile anaesthesia may benefit elderly people who are considered vulnerable to excess or insufficient sedation, due to their reduced ability to eliminate and excrete drugs, may benefit from this technology through sedation becoming more easily monitored and titrated. Pregnancy and age are protected characteristics under the 2010 Equalities Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	AnaConDa-S has been significantly reduced in the volume of the device compared to the original AnaConDa device. This allows it to be used in children and young people with small/minute tidal ventilation. Age is a protected characteristic under the Equality Act 2010.	
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

AnaConDa-S for sedation with volatile anaesthetics in intensive care

1 Technology

1.1 Description of the technology

The Anaesthetic Conserving Device-S (AnaConDa-S; Sedana Medical) is a volatile anaesthetic delivery system to give isoflurane or sevoflurane to people who are invasively ventilated, usually in an intensive care setting.

AnaConDa-S is a single-use device (replaced every 24 hours or when needed). The device can be inserted into either the breathing circuit of a ventilator between the endotracheal tube and Y piece, replacing the heat and moisture exchanger (standard placement) or in the inspiratory port of the ventilator (alternative placement). Liquid anaesthetic is injected through the anaesthetic agent line, into a porous rod in the AnaConDa-S device where the anaesthetic is vaporised. The vaporised anaesthetic is then inhaled by the patient with the inspiration flow from the ventilator. With continued breathing, the majority of anaesthetic agent that has not been absorbed by the lungs is exhaled and adsorbed by an active carbon filter in the device. On further inhalation, the anaesthetic is desorbed from the filter and transported back to the lungs, reducing the amount of anaesthetic agent wasted. The AnaConDa-S device also contains a bacterial and viral filter and a gas analyser port. This port is used to measure the exhalated anaesthetic concentration in minimal alveolar concentration (MAC value; a relative measure of the level of anaesthesia) or end-tidal concentration (Fet%). Side stream or mainstream

gas monitors, which can measure concentrations of carbon dioxide and anaesthetic gases, must be used to continually monitor anaesthesia, these will need to be purchased separately if not already available.

AnaConDa-S can be used with almost any kind of ventilator, except high-frequency ventilators. It was launched in the UK in 2017 and is a newer version of the AnaConDa device (available in the UK since 2005), which is now only available on request in the UK. The AnaConDa-S has a lower dead space of 50 ml (compared with 100 ml in the original device) and works with tidal volumes as low as 90ml. The lower dead space allows AnaConDa-S to be used on smaller adults or children who have smaller minute or tidal ventilation.

1.2 Relevant diseases and conditions

The AnaConDa-S is intended for delivery of volatile anaesthetics as an alternative to IV sedatives for sedating people who are invasively ventilated in intensive care. The AnaConDa-S has a tidal volume working range of 200 ml to 800 ml when used in standard placement. Small tidal volume (90 ml) can be achieved when AnaConDa-S is used in the alternative placement. Volatile anaesthetics should not be used in people with a known history of malignant hyperthermia. Using volatile anaesthetics in pregnant women, especially in the first trimester, could have potential teratogenic or developmental effects on the unborn baby. The AnaConDa-S system could be used for people who need more rapid awakening for assessment; in people with difficult or limited IV access; or to manage sedation in cases when sedation is difficult despite using multiple sedative agents. Volatile anaesthetics can also be used to treat bronchospasm in mechanically ventilated people with severe acute asthma and in sedating mechanically ventilated people with acute respiratory distress syndrome (ARDS).

Most mechanically ventilated people receive sedatives to keep them comfortable and to facilitate treatment when in intensive care. A systematic review reported that there was a substantial incidence of sub-optimal sedation

in people in intensive care unit (ICU) with a greater tendency toward over-sedation.

1.3 Current management

Adults who need sedation in intensive care are sedated using IV sedatives and analgesics, primarily propofol or midazolam with alfentanil or morphine. Children in intensive care usually have sedation with IV midazolam and morphine or fentanyl.

The Intensive Care Society's 2014 (update to be published in 2021) review of best practice for analgesia and sedation in ICU states that there was insufficient evidence to recommend a particular sedation regimen and that the type of sedation should be individualised to the patient's requirements and situation. However, it also notes that the current evidence supports modest benefits in outcomes with non-benzodiazepine based sedation versus benzodiazepines.

The guideline also states that there are difficulties in delivering and scavenging volatile anaesthetics. There are also concerns about fluoride accumulation (with sevoflurane use) and the dependency of ventilation. Delivery devices, such as AnaConDa-S, as well as scavenging systems, make using isoflurane and sevoflurane in intensive care safer for staff. Isoflurane has shown safe, effective sedation for up to 96 hours in small studies, with faster awakening than midazolam. Isoflurane has shown similar awakening to propofol. Isoflurane is also a potent bronchodilator and is valuable in treatment for status asthmaticus.

AnaConDa-S is for use by healthcare professionals, trained to use inhalational anaesthetic drugs and recognise and manage any adverse effects, in an intensive care setting. In the NHS this would likely be intensivists and intensive care nurses. Usually sedation parameters (such as Fet% and MAC) would be set by an intensivist and modified if needed by nurses. Administration of isoflurane and sevoflurane using AnaConDa-S should only

be done in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function.

The following publications have been identified as relevant to this care pathway:

- BNF treatment summary on anaesthesia (general).
- BNF for Children treatment summary on anaesthesia (general).
- Sedation for patients in ICU. Intensive Care Society Guideline.
- Medication concentration in critical care areas. Intensive Care Society Guideline
- British guideline on the management of asthma. British Thoracic Society and Scottish Intercollegiate Guidelines Network
- Guidelines on the Management of Acute Respiratory Distress Syndrome (ARDS). The Faculty of Intensive Care Society and Intensive care Society, supported by British Thoracic Society.

1.4 Regulatory status

The AnaConDa-S received a CE mark in February 2017 as a class IIa device under the EU MDD 93/42/ECC.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Shorter, more predictable wake up time after ICU sedation and avoidance of slow sedative excretion and slow emergence from sedation
- Reliable, sustainable sedation efficacy (comprised of time to extubation, proportion of time within desired sedation level, titration ability)
- Potential reduction in markers of cardiac, liver, gut, kidneys and brain injury
- Effective sedation in patients with life-threatening bronchospasm and asthma
- Improved oxygenation through improved gas exchange
- Improved cognitive recovery/psychological outcomes (e.g. reduction in memories of hallucination, and long-term psychological morbidity)

- Increased rate of spontaneous breathing, resulting in preserved respiratory muscle function
- Reduced dose and less frequent use of opioid administration

The benefits to the healthcare system claimed by the company are:

- Shorter duration of mechanical ventilation and increased ventilator-free days
- reduced length of stay in the ICU and in hospital
- Reduced costs compared with IV sedation
- Reduction in staff time for daily IV sedation interruption and sedative administration.

The sustainability benefits claimed by the company are:

- Reduction in volatile anaesthetic use via the anaesthetic conserving function of AnaConDa-S.
- Replacement for the need of a 'wet circuit', its associated consumables and energy resource requirements.

2 Decision problem

Population	People who are invasively ventilated in intensive care using a mechanical ventilator but not a high frequency ventilator.
Intervention	AnaConDa-S AnaConDa (previous version)
Comparator(s)	IV sedatives Standard vaporiser
Outcomes	The outcome measures to consider include: • wake-up time after ICU sedation • cognitive recovery • sedation efficacy (time to extubating, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale) • markers of cardiac injury, liver, gut, kidneys and brain for short-term operative sedation

	• sedation effectiveness in patients with life-threatening bronchospasm and asthma • oxygenation and inflammatory markers in patients with ARDS • psychological outcomes (e.g. memories of hallucination, and long-term psychological morbidity, PTSD) • Effectiveness of ventilation on people with bronchoconstriction • Reduction of additional bronchodilators • duration of mechanical ventilation/ increased ventilator-free days • length of stay in the ICU. • hospital length of stay/ hospital-free days. • Amount of volatile anaesthetic agent used • Staff exposure to volatile anaesthetic agents • Staff time in the ICU • Amount of opioid drug used • Device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• People with acute asthma that need to be mechanically ventilated. • People with acute respiratory distress syndrome that need to be mechanically ventilated • Children that need to be mechanically ventilated • Patients who need to have regular neurological wake up tests performed. • People who are intolerant to IV sedation (e.g people who misuse alcohol, people who misuse drugs, people on overdose, people with COVID-19) • People with hepatic and renal failure • People with super-refractory status epilepticus • People under prolonged sedation who need an IV sedation break (due to being at risk of developing tolerance, tachyphylaxis and/or propofol infusion syndrome)
Special considerations, including those related to equality	Volatile anaesthetics may not be suitable for pregnant women. Volatile anaesthesia may particularly benefit children for whom sedation is difficult. Volatile anaesthesia may benefit elderly people who are considered vulnerable to excess or insufficient sedation, due to their reduced ability to eliminate and excrete

	drugs, may benefit from this technology through sedation becoming more easily monitored and titrated. Pregnancy and age are protected characteristics under the 2010 Equalities Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	AnaConDa-S has been significantly reduced in the volume of the device compared to the original AnaConDa device. This allows it to be used in children and young people with small/minute tidal ventilation. Age is a protected characteristic under the Equality Act 2010.	
Any other special considerations	Not applicable	

3 Related NICE guidance

Published

- Bronchial thermoplasty for severe asthma (2018) NICE interventional procedure guidance IPG635.
- Extracorporeal membrane oxygenation for severe acute respiratory failure in adults (2011) NICE interventional procedure guidance IPG391.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Academic Paediatrics Association of Great Britain and Ireland
- Anaesthetic Research Society
- Association for Paediatric Emergency Medicine
- Association of Anaesthetists

- Association of Anaesthetists of Great Britain & Ireland
- Association of Paediatric Anaesthetists of Great Britain and Ireland
- Neuro-Anaesthesia and Critical Care Society of Great Britain and Ireland
- Royal College of Anaesthetists
- Paediatric Intensive Care Society
- Royal College of Paediatrics and Child Health
- Intensive care society
- British Paediatric Respiratory Society

Adoption report: MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Summary

Adoption levers identified by contributors

- Provides an alternative option for sedation: useful if there is a shortage of IV sedative agents, if IV drug combinations may have adverse effects or if numerous agents are needed to sedate a person effectively and if there is little or no IV access.
- Less side effects than IV sedation.
- Could be cost saving if replacing numerous sedation agents leads to a reduction in the adverse effects of IV sedation and reduces intensive care (ICU) length of stay.
- May better control sedation depth.
- Could reduce capacity needed and potential for error when amending IV sedation.
- Faster awakening time.
- Volatile anaesthetics act as a therapy for people with asthma.
- Can be used with standard ventilators.
- May be used to sedate and act as a therapy for people with COVID-19 and or hypoxia.

Adoption barriers identified by contributors

- Training required to overcome barriers and to monitor patients, particularly for nurses and non-anaesthetists.
- Need for additional gas monitoring not widely used or set up in ICU.
- Beliefs about need for active gas scavenging and concerns regarding environmental impact.
- Economic savings are difficult to demonstrate.
- Possible exposure to volatile anaesthetics for staff.
- Possible problems with humidification tube blockage.
- Lack of evidence comparing the use of this device with IV sedation in ICU.

Issue date: May 2021

1 Introduction

The adoption team has collated information from 9 healthcare professionals (7 consultants and 2 nurses) working within NHS organisations. Seven of these have experience of using AnaConDa-S. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

AnaConDa-S was launched in the UK in 2017 and is a newer version of the AnaConDa device (available in the UK since 2005), which is now only available on request in the UK. The company report the system is used in around 40 NHS hospitals in England.

2 Contributors

Details of contributing individuals are listed in the below table.

Job title	**AnaConDa-S user and length of use**
Lead critical care consultant	Yes- for 10 years
Intensive care nurse	Yes- within the last year
Consultant in anaesthesia & critical care medicine	Yes- for 2 years
Consultant cardiothoracic anaesthetist	No
Consultant paediatric intensivist	Yes- for over 12 years
Consultant neuro anaesthetist	No
Practice development nurse	Yes- within the last year
Consultant in anaesthesia and critical care medicine	Yes- on and off for 10 years
Consultant paediatrician	Yes- within the last year

3 Current practice in clinical area

Contributors reported that ventilated adults requiring sedation in ICU are routinely sedated using IV anaesthetics: primarily propofol with an opiate (alfentanil, fentanyl, remifentanil or morphine). Dexmedetomidine, clonidine and midazolam are other sedative agents used but are not first line. One contributor reported that they have not used midazolam for many years due to it causing delirium. However, another contributor reported using midazolam if a person requires long term sedation as propofol should not be used long term. Dexmedetomidine is reported to be expensive. Sometimes people could be given 3 to 4 agents to reach an acceptable level of sedation.

Ventilated children requiring sedation in ICU are reported to be sedated with midazolam and morphine or fentanyl. Again, children can sometimes require a few agents to sedate them appropriately. Propofol is not used as a sedative agent in people under the age of 16.

IV sedation is associated with side effects which are more significant the longer a person is sedated. Contributors reported that IV sedatives are metabolised and slowly cleared from the body leading to accumulation. This results in slow awakening and adverse impacts on blood lipids, the liver and the kidneys.

One contributor explained that IV sedation is not managed well and that oversedation is a problem. They explained that in some cases the effects of IV sedation are still evident 3 to 4 days later due to over sedation.

4 Use of AnaConDa-S in practice

All contributors, including those who have used it for a long time, described the technology as novel which demonstrates a delay in innovative technology being accepted and adopted within NHS practice. A regulatory issue relating to use of volatile anaesthetics for sedation in ICU may also contribute to this delay. There was

variation in both frequency and indication for use. Some have used the device in very specific patient groups including people who:

- have been or will need to be sedated for a long time and have become dependent on IV combinations
- are known drug users
- have asthma and are experiencing bronchospasm
- have little or no IV access
- have COVID-19
- are difficult to sedate (children and people with COVID-19 were specifically mentioned as difficult to sedate).

Others have used the device in a wide range of people. One contributor indicated they would only use it in people with healthy lungs and 4 others have used it to sedate and act as a therapy for people with COVID-19.

Another disparity reported was level of sedation. Some reported they would use the device when they needed a deep level of sedation whereas others used when a light sedation level was required. All agreed that with AnaConDa-S the level of anaesthetic required for the desired level of sedation can be accurately measured and monitored which is a benefit.

Two contributors who had not used AnaConDa-S frequently reported that it was underused and that they could use it more. They explained that there wasn't a specific reason for this and put it down to ease of maintaining current practice.

Two contributors had started using the device to ensure they had an alternative method of sedation in the event of a propofol shortage (following a warning about this) and during the COVID-19 pandemic. Despite the warning no shortages of propofol have been experienced.

The fact that AnaConDa-S can be used with standard ventilators was reported to be a benefit. Previously, if volatile anaesthetics were used in ICU, older and bulky anaesthetic machines would be used. This resulted in time wasted trouble shooting unfamiliar machines. Using AnaConDa-S removes this barrier.

Most contributors reported using the volatile anaesthetic isoflurane as it is cheaper than sevoflurane. Only one contributor used sevoflurane.

The following conditions were given as possible contraindications for sedation with AnaConDa-S by contributors:

- malignant hyperpyrexia
- impaired liver function
- circulatory problems
- cancer
- raised intracranial pressure
- epilepsy.

5 Reported benefits

The potential benefits of adopting AnaConDa-S, as reported to the adoption team by the healthcare professionals using the technology are:

- Provides an alternative option for sedation. This is useful if there is a shortage of IV sedative agents, if IV drug combinations may have adverse effects, if numerous agents are needed to sedate a person effectively or if there is little or no IV access.
- Could be cost saving if replacing numerous sedation agents leads to a reduction in the adverse effects of IV sedation and reduces ICU length of stay.
- May better control and maintain sedation depth and have less adverse effects than IV sedation (nightmares, confusion, hallucinations, disorientation, impact on development in children, impact on blood lipids, liver and kidneys).
- Could reduce staff capacity needed and potentially reduce error when amending IV sedation. IV sedation needs to be checked and topped up/amended every 30 to

60 minutes. AnaConDa-S is changed every 24 hours and the volatile agent syringes are changed on average every 7-12 hours depending on infusion rate.

- May result in a faster awakening time. Sedation wears off as soon as the volatile anaesthetic is exhaled. Contributors reported that patients can be sat up in bed and talking within 5 minutes.
- Volatile anaesthetics act as a first line therapy for people with asthma as they are potent bronchodilators.
- Can be used with standard ventilators which are currently widely used in ICUs.
- May be used to both sedate and act as a therapy for patients with COVID-19 and or hypoxia.

6 Insights from the NHS

Clinician confidence/acceptance

Using volatile anaesthetics in ICU

Contributors reported that whilst volatile anaesthetics are used frequently in theatre, they are not widely used in NHS ICUs and their use in this setting is viewed as a significant change to standard practice. For this reason, contributors explained that there is a lack of understanding regarding their utility in ICU. One contributor considered that this had improved during 2020 as many of the reserve list of staff brought into ICU to help look after people with COVID-19 had theatre backgrounds and were familiar with the use of volatile anaesthetics. If adopted, standard operating procedures (SOP) may need to be developed for both the set up of the device and the administration of the volatile agent. The company reported that they share a generic SOP when the device is purchased.

It was reported that sedation depth can be better controlled and maintained with volatile anaesthetics which is good for ventilated patients in ICU as they usually do not need a deep level of sedation. Contributors explained that this will help to prevent over sedation.

One contributor from a rural hospital indicated that change from entrenched IV sedation practice will be a challenge and that they have now reverted to IV sedation.

This site had used the device in one person with medical complications due to COVID-19. This same contributor explained they faced challenges related to its licence for use in ICU in their area.

Gas scavenging

The need for gas scavenging when using volatile anaesthetics was raised by contributors as a potential barrier. Potential users will need to understand that AnaConDa-s has an inbuilt passive scavenging filter to absorb waste anaesthetic gas into a charcoal canister, removing the need for ICU to have active gas scavenging systems in place. It was reported that there is likely to be a misunderstanding about this amongst the ICU community.

One contributor explained that their unit had active gas scavenging built in when it was rebuilt 15 years ago to enable the use of volatile anaesthetics in ICU. However, when using AnaConDa-S, the passive scavenging filter included with the device is used as it is more convenient than plugging the ventilator into the active gas scavenging system.

One non-user, has conducted a study about the use of volatile anaesthetics and air pollution in the recovery setting. This indicated that people continue to exhale volatile agents in recovery areas which do not have scavenging systems.

Change and disposal of the scavenged gas canisters was reported to be straightforward. They can be disposed of in general hospital waste. Contributors reported that canisters need to be changed after a certain amount of volatile anaesthetic syringes had been used and that a record was kept ensuring this happened at the right time.

Environmental impact

Concerns about the environmental impact of using volatile anaesthetics was a consistent theme. However, the anaesthetic conserving function of the device was reported to lead to a reduction in the amount needed and the passive scavenging filter may reduce the environmental impact as excess gas is not released into the atmosphere. It was reported that this is likely to be a historical concern and that

recent research has demonstrated that the impact of volatile anaesthetic use on the environment, when released into the atmosphere, (which does not happen when using AnaConDa-S) is not as significant as it was once thought to be.

The volatile anaesthetics used with AnaConDa-S (isoflurane and sevoflurane) were reported to be less polluting than other volatile agents e.g., desflurane.

Cardiovascular side effects

There are concerns regarding the cardiovascular (CV) side effects of using volatile anaesthetics from contributors. One contributor reported that all types of sedation have CV side effects and that ICU staff just need to be aware of and prepared to deal with these. CV side effects mentioned by contributors are hypotension, tachycardia, and bradycardia.

Fluoride build up

Three contributors explained that there may be a theoretical concern regarding a build-up of fluoride when using the volatile anaesthetic sevoflurane. This was not something that had been witnessed but was a concern raised within literature and may act as a barrier to uptake.

Humidification tube blockage

One contributor explained that the biggest barrier for their unit has been problems caused by blockages in the humidification tube. They indicate that this may be caused by staff not disconnecting the heat and moisture exchanger when setting up this device. Another contributor reported that prompts to turn the humidifier off when setting the device would be useful.

Resource impact

Sidestream or mainstream gas monitors must be used with the device. Most ICU monitors do not have this function and new or additional monitors or software will need to be purchased. This will be an initial outlay for units wanting to adopt AnaConDa-S. One contributor reported borrowing gas monitors from the company and then purchasing them. Another reported borrowing monitors from theatre and that using these was a challenge as they had not used them before. One contributor

explained that they purchased new monitors when preparing for COVID-19 which may mean this is not as significant an issue, as other ICUs could have done the same when preparing for the pandemic. The company's gas monitors were reported to be around £2500 and ICU machines with gas monitoring ability were reported to be around £5000.

Most contributors thought using the device could be cost saving if it replaces the need for numerous sedation agents (in particular dexmedetomidine) and there is a reduction in the adverse effects of IV sedation leading to reduced time to extubation and reduced ICU length of stay. One contributor reported its use as very expensive and that they needed to use the device in combination with IV sedation as patients kept waking up. This contributor used the device only in people with COVID-19 and reported they needed lots of sedation.

The company report that it is difficult to demonstrate economic savings due to the inherent difficulties of running RCTs in ICUs for more than only a short amount of time.

Training

Training in how to use the device and about volatile anaesthetics will be needed. Doctors with an anaesthetic background will be familiar with volatile anaesthetics. Non anaesthetic ICU doctors and nurses will generally be less familiar with them and will be trained in IV sedation only. Contributors explained that the device will usually be set up and maintained by nurses.

The company provides well reviewed e-learning with CPD accreditation followed up with bedside learning with a company representative attending the ICU. The company provide training at no cost to new users. Contributors indicated that this training was good and that they felt proficient in using the device once training was complete.

A starter pack is provided by the company which contains everything needed and information which reiterates the training and provides guidance on doses.

The device was reported to be easy to set up.

Clinician safety

Contributors discussed the possible impact of exposure to volatile anaesthetics for staff. The impact of this long term is not known but all users reported that exposure was minimal. Volatile agent bottles and syringes are colour coded and specific. The device recirculates what is exhaled, and any waste anaesthetic is absorbed into the passive scavenging canister. There may be some exposure when the circuit is broken such as to clean tubes. One contributor explained that if any volatile agent is spilt, charcoal from a passive gas scavenging canister can be thrown over the spillage to quickly absorb the volatile agent.

Contributors reported that the device and empty syringes can be disposed of in the general hospital waste. Syringes with residual anaesthetic gas should be disposed of through special hospital waste. Any glass bottles containing anaesthetic residue are incinerated. No barriers were raised regarding disposal.

Patient selection

Patient selection varies amongst contributors.

One contributor reported that as volatile agents are vasodilators, there may be issues with using them in people with circulatory issues. However, another contributor commented that this is also a consideration when using propofol. Also referred to was a paper detailing that using volatile agents in people with cancer may be associated with higher tumour spread rates.

Four contributors had used the device in patients with COVID-19 to sedate and act as a therapy to improve oxygenation. As volatile anaesthetics are powerful bronchodilators and vasodilators, the hope was that oxygen requirements would be reduced. This was seen in some patients. For this same reason, contributors suggest that volatile anaesthetics can help treat people with hypoxia.

Prescribing

One contributor reported that the standard prescription chart used prior to adopting AnaConDa-S did not include inhaled gases. Medical gases should be prescribed and a gas prescription chart detailing inhaled gases, nebuliser and oxygen was developed.

The company provide a dose range guide with the device. It was reported that it is important for users to see these as a guide and not as limits because some patients may need more than the guide suggests to reach the required level of sedation.

7 Comparators

One contributor mentioned upcoming technology from Baxter and Sagetech which utilises charcoal filters to absorb volatile gases which can be later reprocessed for re-use thus reducing their unfavorable carbon footprint. AnaConda-S is similar in that it also uses a charcoal cannister for absorption.

NICE National Institute for Health and Care Excellence

Cedar
Healthcare Technology Research Centre

External Assessment Centre correspondence log

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*

1.	05/05/2021	Company engagement meeting - Clinical	Start-up videoconference with the company. A list of questions was sent to the company in advance of the meeting.	Full responses, verified by the company are detailed in Appendix 1.
2.	12/05/2021	Clinical expert engagement meeting	Videoconference conference with a range of clinical experts to discuss questions relating to the company's clinical submission.	Full responses verified by experts are detailed in Appendix 2. Appendix 3 shows a written response given by one of the experts to the questions discussed at the meeting.
3.	12/05/2021	Company - clarification	The EAC asked for some clarification regarding the CE status of the device	Sedana Medicals response: • We will by September have a designated Responsible Person in UK to comply with new rules. • There is a transition period for the change of CE mark to new UK mark until 2023. We will keep the CE mark on AnaConDa until then and will change/add the new UK mark on the product at that time. The company also provided references to two studies they mentioned during the company engagement meeting: https://pubmed.ncbi.nlm.nih.gov/33528922/ https://pubmed.ncbi.nlm.nih.gov/31112380/
4.	12/05/2021	Company - clarification	The EAC identified some papers in the literature from before 2005 that refer to an Anasthetic Conserving Device (Hudson SCI, Upplands Vasby, Sweden) and asked if this was the same device as the original	The company confirmed that this is the same AnaConDa device. Hudson RCI was a previous owner of this, and it was eventually acquired by Sedana Medical.

			AnaConDa with the 100ml dead space, a predecessor device or a completely different device.	
5.	26/05/2021	Clinical experts – information required	The clinical experts were asked to state five outcome measures that they believed to be most important.	Expert responses, from all seven experts, together with the exact question asked, are presented in Appendix 4.
6.	01/06/2021	Clinical experts – information required	The clinical experts were asked to comment on the relevance of presenting data specific to cardiac surgery patients and whether this subgroup would be representative of short-term sedated patients. They were also asked on the potential benefit of discussing separately long- and short-term sedated patients.	Expert responses, from the four experts that have replied, together with the exact questions asked, are presented in Appendix 5.
7.	04/06/2021	Company engagement meeting - Economic	Start-up videoconference with the company. A list of questions was sent to the company in advance of the meeting.	Full responses, verified by the company are detailed in Appendix 6.
8.	10/06/2021	Clinical experts – information required	The clinical experts were asked a range of questions regarding to the use of sedative and analgesic medication, the importance of mortality as an outcome measure as well as to how the AnaConDa is set-up on patients in their institution.	Expert responses, from the five experts that have replied, together with the full list of questions, are presented in Appendix 7.

9.	16/06/2021	Company - clarification	The company was asked to provide additional information on the staff training that they offer to ICU staff who will be using the AnaConDa-S. The company was also asked how it costed propofol and nurse time cost in their model.	The company's full response is presented in Appendix 8.
10.	17/06/2021	Company - clarification	The company was contacted regarding the Sackey 2018 study (Sackey is the company's chief medical officer). Since only an abstract was available for that study, the following questions were asked: • Is there are full publication planned/submitted? • If so could you please share a draft of the full publication? • Could you please give some information around the outcome 'Reduction in in-patient deaths' and how that is being attributed to inhaled sedation with AnaConDa?	The following answer was provided: The ISPOR poster was produced by a health economist team we used in an earlier phase when we did not have own data available. I do not believe we have included it in the package to you. It has not been expanded to a full-length publication. The poster uses the odds ratio for mortality based on the Bellgardt et al. 2016 study. Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients: Retrospective analysis - PubMed (nih.gov) Hospital mortality (primary) and 365-day mortality (secondary) were compared with the Kaplan–Meier analysis and a log-rank test. Adjusted odds ratios (ORs) [with 95% confidence interval (95% CI)] were calculated by logistic regression analyses to determine the risk of death after isoflurane sedation. These ORs were then used to estimate the UK modelled scenario.

11.	23/06/2021	Company - clarification	1. Can you please state Sedana's justification for the model assumption that 'IV sedation requires more frequent dose renewal? 2. Can you please state Sedana's justification for the model assumption that 'Daily sedation interruption protocols are more likely with IV sedation' 3. Can you please confirm that the economic model is based on AnaConDa-S costs (rather than the old 100ml dead space model)? We do not need very long answers for the first two questions - a couple sentences will do.	For number 1 and 2 I would refer to the clinical validation, we spoke to a UK clinical KOL who immediately listed these 2 aspects as potential practical advantages. For #1 you can see that the vial size for propofol and the dose means that to keep the patient sedated requires more dose renewals – changing for the next vial to continue the sedation. For #2 we also reference the guidelines (like PADIS) that recommend DSI to avoid accumulation and over-sedation using IV Price of the AnaConDa-S is what we provided, the other components can be used for either.

Appendix 1: Notes from Company Post Clinical Submission Meeting for MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

This document summarises the discussions that took place at the company post clinical submission meeting for MT582 AnaConDa-S, which took place on Wednesday 05th May 2021, 1:30-2:30pm. Written responses were supplied by the company in advance of the meeting on 4 May 2021.

Attendees

NICE

1. Kimberley Carter, Health Technology Assessment Adviser
2. Federica Ciamponi, Health Technology Assessment Analyst

Cedar (EAC)

3. Susan O'Connell, Senior researcher
4. Laura Knight, Senior Researcher
5. Michal Pruski, Researcher
6. Rhys Morris, Cedar Director
7. Sarah Kotecha, Researcher

Company

8. Paul Miller, Consultant for Sedana
9. Christian Malin, Country Manager
10. Jens Lindberg, Vice President Commercial Operations
11. Joanne Lessells, Medical Science Liaison
12. Per Svangren, Consultant for Sedana
13. Peter Sackey, Chief Medical Officer

Themes for discussion

1. Device Specific
2. Clinical
3. General
4. Other Discussed Issues

Device Specific

1. Can the company give a brief overview of the device and how it works including any component parts (including which parts necessary for set-up come supplied in the AnaConDa starter pack and which do not, and which replacement components would be needed for ongoing care).

Written response:

AnaConDa is a small device which is inserted in the breathing circuit between the ET-Tube and the Y-piece. The simple design of the AnaConDa incorporates a unique miniature vaporizer and an anaesthetic reflecting filter which makes it possible to deliver anaesthetic agents in a simple and efficient way.
To start the therapy on a patient we would recommend a starter kit for the first 24 hours. There is no premium associated with the “kit” however it does simplify set-up and ensure all components are at the bed-side, with no frustrating omissions or confusion. Full descriptions, pictures and pricing of each component is attached and detailed below:

The AnaConDa starter kit contains:

- AnaConDa-S
- FlurAbsorb-S
- FlurAbsorb-S mount
- FlurAbsorb accessory k
- Gas sample line
- Nafion line
- AnaConDa syringe
- Single-use filling adapter with standard threading

To continue therapy, further syringes will be required. Typically, with an Isoflurane infusion rate of 5ml per hour this would see a second syringe being used at 12 Hours. (2 syringes per day). Sevoflurane may see a higher infusion rate.

Day 1			Day 2 +	
				AnaConDa-S
	Starter Kit			FlurAbsorb-s
	Syringe			Syringes

Additional discussion
Company noted that the price of the kit is slightly cheaper than that of buying the component parts separately.

2. Can the company comment on the difference between standard and alternative placements of the device in terms of
   a. Choice of placement

Written response:

i. Tidal Volumes off less than 200Ml where dead-space should be reduced as much as possible would align with our recommendations for alternative placement.

b. Impact on device efficacy – in the alternative placement the device will not be able to perform its anaesthetic conservation function in this position or provide its heat and moisture exchanger (HME) function; moreover, there will be a higher leak of the anaesthetic agent into the environment.

Written response:

i. With alternative ventilator placement, reflection is lost. However, with associated small tidal volumes (VT) necessitating this placement infusion rates are low (based on MV) therefore consumption / pump rates are similar.

ii. As with standard placement the FlurAbsorb is positioned to absorb the exhaled volatile agent. This does not change with placement however the FlurAbsorb is changed more frequently.

iii. In alternative placement the use of active humidification is recommended.

Additional discussion

Company noted that the device can act as an HME and that in the standard placement AnaConDa provides about 90% of sedative reflection, but that this is lost in the alternative placement. Company notes that due to the placement on the alternative position due to a need for low deadspace the HME would not be used, just active humidification. Infusion rates of the sedative when the AnaConDa is placed in this position would also be low due to it being used in patients require small tidal volumes (e.g. patients on extracorporeal membrane oxygenation [ECMO] or physically small patients), so the amount of the sedative leaking from the ventilator would be low.

c. What proportion of incidents the device is used in each position?

Written response:

i. *Currently there are three paediatric intensive care units (PICU's) utilising AnaConDa-S in PICU a proportion of their patient population would use this set-up where small tidal volumes dictate.*

Additional discussion

No data available regarding this. Positioning is patient dependent and will be based on tidal volumes. It is very rarely used on the ventilator side and might be used in adult patients who are on ECMO.

d. Additional connectors needed to connect side-stream multi-gas monitoring in the alternative position as the sampling line cannot then be connected to the AnaConDa device itself

Written response:

i. *Usually a leur-lock port at the wye piece is an integral part of the circuit and can be used for this purpose.*

3. Is the FlurAbsorb filter still available in both large and small sizes? If so, does the large filter need to be replaced every 24 hours too or is it done by weight increase of the used absorber compared to when it is new?

Written response:

a. *The larger FlurAbsorb is still available and requires change less frequently due to its larger capacity this can be based on weight or syringe number.*

Additional discussion

There is a price difference between the two sizes and the economic model will be transparent around which version is costed. FlurAbsorb does not need to be changed every 24 hours compared to FlurAbsorb-S. FlurAbsorb has a capacity of 10 syringes (5 if AnaConDa is in the alternative placement; it weights 1000g when empty and 1400g when full). FlurAbsorb-S needs to be changed when it reaches syringe capacity and at least once in a 24h period. The company will send through details of the packs/filters and capacities.

4. Do the FlurAbsorb filters need to be ordered separately.

Written response:

a. FlurAbsorb-S is included in the starter kit (as detailed in 1, above). The starter kit is designed for the initial start up of a patient on AnaConDa

Clinical

1. Can the company comment on how long on average, sedation might be needed for a mechanically ventilated patient?

   Written response:

   a. *This would be based on the NHS published data for intensive care unit (ICU) admissions and bed occupancy and is dependent of reason for admission.*

   Additional discussion

   Company will provide data for AnaConDa and comparator (propofol) from SED-001 trial carried out in Germany. This will be the economic base case, which will be supplemented with observational data from another study where midazolam was used. The company noted that length of stay varies from patient to patient, including the reason for the admission and the reason for sedation, and that IV agent use can be associated with sedative accumulation resulting in delays in patient weaning or wake-up. As such, volatile sedation can facilitate faster wake-up times and potentially result in less staff input.
   The company was also asked what they consider to be standard-of-care. They consider it to be propofol, but acknowledges varied clinical practice including the use of opioids and other analgesics in normal care.

2. Use of HME management of humidification is generally not thought to be suitable for some groups of patients who require a wet circuit. AnaConDa cannot be used with a wet circuit, so how does it limit the usefulness of the device in clinical practice.

   Written response:

   a. *The AnaConDa is an advanced HME providing humidification (though this is due to avoidance of moisture loss; tested according to ISO 9360-1) at 34mg/L which is within the American Thoracic Society 2012 guidelines for humidification. With regards to humidification, AnaConDa outperforms other HMEs. In the alternative placement a wet circuit can be used if clinically required*.

3. The company noted that AnaConDa cannot be used with high frequency oscillation. How does it affect delivery of nitric oxide therapy or other drugs that might be delivered directly into the ventilator circuit, e.g. via an aerosol delivery system that would usually slotted into the ventilator circuit.

   Written response:

   a. *This remains unchanged. Nitric is generally used as a potent bronchodilator and therefore its use may not be required alongside the use of volatiles – however both are compatible. Nebulisers should be given proximally to the patient due to the AnaConDa membrane preventing delivery if placed distal to the device.*

4. Company notes that anaesthetic machine use is 'on bulky, impractical, and expensive', but does it know how commonly it used in ICUs for the purpose of delivering volatile anaesthesia?

Written response:

a. *Clinically there may be a desire for the therapeutic benefits associated with volatile delivery, however the above noted restraints as well as the lack of AGSS and Nurse training / competence make this clinical decision impractical in most instances. Incidence will vary from Trust to Trust and may involve the patient being transferred to theatre to deliver inhaled sedation as a rescue therapy.*

5. What anaesthetic/combination of anaesthetics does the company believe to be the standard of care, as the referenced studies seem to use propofol or midazolam or a combination of these?

Written response:

a. *With anaesthetics no other IV sedation is required. With IV Sedation polypharma is common and would again vary from Trust to Trust. Details should be sought from individual clinicians. There is no UK wide sedation guideline, so practice will vary accordingly. The company also noted that the use of volatile sedation is associated with lower doses of opioid analgesics and smooth muscle relaxation.*

6. The submission mentions sedation efficacy, but are there any IV agents that are likely to have to be administered concurrently with iso/sevoflurane to maintain the other components of the triad of anaesthesia in patients managed with the aid of the AnaConDa (including those requiring pharmacological paralysis)?

Written response:

a. *Patients should be sedated to the required level. Patients will continue to need IV opioids as part of their pain management, but studies suggest their use is reduced by 50%. Neuromuscular blocking agents should not be needed if patients are adequately sedated. Also Inhaled anaesthetics have a relaxation effect on smooth muscle therefore patients do not routinely require neuromuscular blocking agents. Which mean spontaneous breathing is possible and reduces atrophy of respiratory muscles.*

7. Section 1 outlining the decision problem highlights that children are a relevant subpopulation, but the search strategy outlined in Appendix 1 seems to exclude evidence concerning children. Is there a reason for this?

Written response:

a. Our own research activities have been limited to Adult patient groups, however we are aware of ongoing paediatric studies.

Additional discussion

The company noted that current regulations do not cover the use of volatile anaesthetics in paediatric ICU sedation, though the device is used in this setting. The company highlighted a blurry line between anaesthesia and sedation in practice. The company believes that there are no publications of comparative studies of the use of AnaConDa in the paediatric population. There might be need of further discussion with NICE as to the inclusion/exclusion of this population from this appraisal.

General

1. The abbreviation PRIS is used in the report. Can the company provide details on this?

Written response:

a. *Propofol Infusion Syndrome which is a common term in ICU.*

2. What does TEAEs mean?

Written response:

a. *Treatment emergent adverse event.*

3. The company state that the clinical trial SED001 is currently academic in confidence (AiC). Could you clarify whether any of the data included in the submission needs to be highlighted as AiC or has only publicly available information been included? Data are highlighted in table 4 but not in the text on page 16 (and various other points through the document, e.g. meta-analysis section).

No written response was given.

Discussion:

Academic in Confidence data is there because SED-001 is still awaiting publication, though there were some press releases regarding it (non-inferiority study that met the primary endpoints). There will be some later revision as to which parts should be marked as confidential and which not. None of the data in the clinical submission is commercial in confidence.

4. In Tables 2, 2a and 6, often other devices (e.g. MIRUS) rather than the AnaConDa are mentioned. Considering that this is a single technology appraisal, are any of these devices'

direct predecessors to the AnaConDa? Or is there another basis on which these devices were deemed to be suitable for inclusion in the evidence?

Written response:

The systematic literature review (SLR) was set up to review RCT evidence directly comparing IV and inhaled sedation in mechanically ventilated patients in the ICU, we did not restrict by drug or by device. All studies are included as relevant to support the use of inhaled sedation.

Discussion:

MIRUS is a completely different device to AnaConDa. Additionally, the search was carried out to include any inhaled anaesthetic, not only Isoflurane or Sevoflurane.

Other Discussed Issues

1. The company noted that they are in the process of filling for the UK conformity assessment.

2. The company clarified that AnaConDa and AnaConDa-S have the same mechanism of action, just different deadspace (100ml vs 50ml).

3. The company was asked to clarify how widely applicable AnaConDa would be in leu of the statement that it would be recommended for patients requiring a Richmond Agitation-Sedation Scale (RASS target) of -2 to -5 for over 12 hours, while most patients seem to be targeted for a RASS score of 0 or -1.

   The company mentioned two studies demonstrating a higher need of sedation in patients than -1 – 0 and the company will provide references to these studies. This higher sedation requirement is potentially due to patients needing to get used to the endotracheal tube and due to all the procedures being carried out at the beginning of an admission. Later on during the ICU stay sedation might be decreased to promote extubation. The company noted that the average RASS in their trial was around -3.2 – -3.3. The company noted that no drug can easily achieve optimum sedation and that inhaled sedatives allow patients to wake up quicker due to no requirement to metabolise the drug.

4. The company was asked to comment on the toxicity associated with volatile anaesthetics.

   The company mentioned malignant hyperthermia (a pharmaco-genetic disorder), it also can happen with suxamethonium. Incidence is somewhere between 1:5000 to 1:50000-1:100000 and occurs mainly during general anaesthesia, with most at risk patients being aware nowadays due to familial history. Long term use of Sevoflurane is also associated with reversible polyuric dysfunction. The company mainly promotes the use of AnaConDa with Isoflurane.

5. The company was asked to comment on any limitations in the use of AnaConDa in those with drug misuse problems.

   The company noted no known contraindications and that the inhaled sedatives have been used in this population. There was some discussion regarding the use of opioids and inhaled sedation with respect to rapid-detoxification and ultra-rapid-detoxification, but the company noted that there probably is little evidence on this issue but this might be a patient group for which inhalant sedation might be particularly indicated. The EAC noted that the opinion of the clinical experts might be needed on this issue, but that this issue is not relevant to the scope of this assessment, but just to confirm that AnaConDa is not contraindicated in this population.

6. The company stated that Paul will be the main contact for the EAC and NICE will provide the contact details.

Appendix 2: Notes from Clinical Expert Post Clinical Submission Meeting for MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

This document summarises the discussions that took place at a meeting with clinical experts after the company's clinical submission for MT582 AnaConDa-S, which took place on Wednesday 12th May 2021, 12:30-1:30pm.

Attendees

NICE

14. Kimberley Carter, Health Technology Assessment Adviser
15. Federica Ciamponi, Health Technology Assessment Analyst

Cedar (EAC)

16. Susan O'Connell, Senior researcher
17. Michal Pruski, Researcher
18. Rhys Morris, Cedar Director

Clinical Experts

19. Dr Jonathan Ball, Consultant in Critical Care Medicine
20. Dr Mark Blunt, Consultant in Critical Care and Anaesthesia
21. Dr Stephen Playfor, Consultant in Paediatric Intensive Care
22. Professor Anil Hormis, Consultant in Anaesthesia and Intensive Care Medicine
23. Dr Guy Glover Consultant in Critical Care and Anaesthesia
24. Dr Paul Dean, Consultant in Critical Care and Anaesthesia
25. Dr Tom Syratt, Cheshire and Mersey Critical Care Network

Themes Discussed

Population
Device

Sedation
Other
General Questions

Population

1. Considering paediatric populations
    a. Do you use the AnaConDa-S in children?
    b. If so, under what circumstances would you use it
    c. How would use in children differ from adults?

As the company's submission concentrated on evidence from the adult population but acknowledged the products use in the paediatric population, the EAC wanted to understand more about the devices use in paediatric patients. The expert commentary was that the device is used frequently in the paediatric setting, with a common use of the alternate placement.
One expert note that the common use of alternative placement in paediatric patients is due to small tidal volumes in these patients. They noted that the manufacturer provides a specification at what cut-off point to change the placement, but it is not a golden rule in clinical practice. 5- or 6-year olds are an approximate cut-off point for positioning the device in the alternative placement. They stated that they use the device in the alternative placement in about 30% of paediatric cases. Nevertheless, AnaConDa is used mainly teenagers, while the bulk of patients on the paediatric intensive care unit (ICU) are 2-year olds. They noted that there are no absolute contraindications in this patient group, save for malignant hyperthermia.

2. Which patient groups are contraindicated for AnaConDa use (e.g. pregnant women, patients with opioid addiction etc).

The EAC wanted to understand if there are any limits to the applicability of the device, especially in reference to equalities considerations. The experts agreed that the only absolute counterindication was malignant hyperthermia but that this pertained to the drugs used with the device and not the device itself.
One expert noted that they tend to use the device as a treatment modality due to the bronchodilatory effect, rather than as a form of sedation. They were not clear why it would be counter-indicated in opioid dependency. They noted that opioids are used in conjunction with volatile agents. In the case of pregnant women they highlighted that this is also not an absolute contraindication but is weighed against the present medical risk to the woman.
Another expert stated that they find the device helpful in cases with opiate addiction as these might fall into the hard to sedate category where volatile agents are helpful. They have also highlighted that volatile agents have been used for a long time in pregnant women. The only potential absolute counterindication of which they were aware was malignant hyperthermia.
The EAC clarified that the EAC did not mean that the use of the device is contraindicated those with opioid addiction problems, but wanted to clarify with the experts whether it was contraindicated in this population due to guidelines on treating those with addiction stating that opioids, in general, should not be completely withdrawn from these patients.

A further expert reiterated similar points to those of the previous expert, but also highlighted that the contraindication is to the drugs not to the device and that relative counterindications pertain to the whole class of these drugs.
One more expert agreed that only malignant hyperthermia would be an absolute counterindication and that there is a distinction between the device and drugs when considering counterindications.

Device

3. How often would you use the alternative placement of the AnaConDa device (can you comment if this proportion of patients would be different in the adult and paediatric populations)?

The EAC wanted to know the frequency of the use of the alternative placement of the device. The use of the alternative placement seems to be common in paediatric patients but not in adult patients.
One expert reiterated the point noted in question 1 about 30% cases using the alternative placement in the paediatric population.
A further expert noted that it is not generally used in the alternative placement, with the exception being e.g. extracorporeal membrane oxygenation (ECMO) patients. The company recommends to use the alternative placement when used in conjunction with Nitric Oxide, but this expert had no experience with it.

Sedation

4. What RASS score is generally aimed/achieved for during sedation?

The EAC wanted to know more about targeting patient sedation, as the company submission stated that the device would be particularly useful in patients requiring sedation for over 12 hours with a RASS target of -2 to -5. Six experts contributed to this question, highlighting the variability in practice, but with a general agreement that RASS is the most common used scoring system in patient, while the comfort score is used in children, and that patients are sedated to various target scores.
The first expert highlighted that the level of sedation aimed for a patient will vary from patient to patient, from -4 up, but that this is a clinical decision. Isoflurane allows a range of scores to be achieved and this will depend on the level of sedation used.
Another expert highlighted that the potential advantage of AnaConDa is that it allows objective assessment of the sedation by monitoring end-tidal concentrations, rather than RASS which is used when using IV sedatives. They also noted that some patients might be in general oversedated.
One more expert noted that, with reference to sedation guidelines, a score of 0 to -1 is very difficult to achieve and not always appropriate.
A further expert added that respiratory failure patients would be a classical example of patients requiring deeper sedation due to induced pharmacological paralysis. They also highlighted that the lung protective function of volatile anaesthetics is also key here.

- *Experts were asked how is the RASS score assessed?*

One expert noted that how to perform a RASS assessment is well described in the literature, recommended for use in the UK and that the scores are recorded by nurses on the patient charts. Another expert stated that in children the comfort score is used rather than RASS, but that there is a lot of variation in practice. They highlighted that doctors rely on a general assessment by the nursing staff on how well the patient tolerates treatment.

- *Experts were asked how useful is RASS scoring?*

One expert noted that when bronchospasmic patients are initially sedated and paralysed, there is an aim for a generally flat patient rather than aiming for a specific score. In these patients, volatile anaesthetics are one of the first things taken off once their condition improves, so there is no further volatile agent use when this scoring comes into play and there is no weaning of these agents as they are replaced by IV sedation.
Another expert countered that in their practice AnaConDa is used routinely and not just on bronchospasmic patients.
A third expert noted that RASS in adults is the best scoring system. Nevertheless, they stated that the utility of these scores is challenging in both assessment and in using them as targets. They also pointed out that sedation is not good if you do not need it.

5. What would you consider the standard of care to be for ICU sedation in adults and children?

The EAC wanted to know what is the most appropriate comparator to AnaConDa. This will help the EAC to assess the clinical evidence with regards to its applicability to the UK and to appraise any economic models. Six experts contributed to the discussion on this point. Propofol came out as the most appropriate comparator to volatile sedatives in the adult population, and that opiate administration would continue with the use of volatile sedation. For paediatric patients it would be midazolam plus morphine or fentanyl.
The first expert highlighted that in reality there is no standard of care with regards to sedation. They noted that a lot depends on personal preference of the clinician, the requirements of the particular patient and what agents are available for use. It is usually an opioid together with a sedative (usually propofol).
Two experts noted the importance of this question as we need to be careful about comparators, as some studies use benzodiazepines which are not particularly relevant to UK practice. They noted that in Europe Midazolam is frequently used but that this is not a first line treatment in the UK, where IV propofol with alfentanyl or fentanyl are the preferred agents, with midazolam considered only further down the line if problems arise with this combination of propofol with an opiate. They highlighted that when you compare volatile compounds to different IV agents, there might be different results/outcomes and that, as such, it is important to use a comparator relevant to UK practice.
Another expert agreed that propofol and an opiate (fentanyl, alfentanil, morphine) is the UK standard of care, and also highlighted that adjunct sedatives (e.g. clonidine) are used during weaning from IV sedatives. They noted that the use of volatile sedation allows one to avoid the used of these sedation adjuncts, simplifying the weaning process.
One expert highlighted that in paediatrics the comparator would midazolam plus morphine or fentanyl, with most units moving to enteral sedation when this becomes appropriate for the patient

and that propofol is not suitable in children. They also noted that there is not much variation in paediatric sedation practice across the UK.

- *Experts were asked about the generalisability of the results from European studies, and between adult and paediatric studies.*

One expert stated that paediatric intensivists are used to extrapolating adult data into paediatric practice. They also noted that in this case this extrapolation might be easier if a lot of trials use midazolam rather than propofol as their comparator with AnaConDa.
Another expert brought to attention that different indications (heart surgery, extracorporeal membrane oxygenation, respiratory patients) will have different outcomes of interest and comparators. They also noted that the patient population will have an impact on the generalisability of the evidence. They also noted that USA guidelines recommend propofol, but that this is just guidance rather than hard and fast rules. A further expert added a guideline of interest here would be the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU guideline from the Society of Critical Care Medicine, which is USA based.

- *Experts were asked if the volatile agent would replace both the sedative and the opiate or just the sedative*

Two experts agreed that propofol would be skipped but the opiate would be kept.
Another expert noted that in paediatrics the opiate would also be skipped, but that is specific to the patient group in which typically volatile sedation is used in the paediatric environment.

6. Do you tend to used Isoflurane or Sevoflurane? What would be the typical (range and average) rates at which these are administered be?

The EAC wanted to know whether one of the two drugs is preferentially used among clinicians and what would be the typical amount of the drug used. Responses from 3 experts suggest that Isoflurane is the volatile agent of choice although Sevoflurane is used in the UK.
One expert stated that they only use Isoflurane with a typical range of 7ml/h to 20ml/h and noted that once a steady state is reached, the typical rate would be 8-10ml/h.
A second expert also noted that they only use Isoflurane in paediatric patients. The expert also noted that their patients (paediatric patients) would already be induced with intravascular (IV) agent and that the only benefit to Sevoflurane would be that patients would be induced using the volatile agent. The expert noted that Sevoflurane has higher associated costs and issues with metabolism.
A third expert stated that they use Sevoflurane at a typical rate of 5 ml/h to 15 ml/h or adjusted to an end-tidal concentration of 1%-3% of Sevoflurane. The expert noted that Sevoflurane might have a better lung protective profile. This expert did state that there may be a switch to Isoflurane in the future however.

Other

7. Are there any iatrogenic effects associated with sevoflurane or isoflurane?

The EAC wanted to know what side effects are associated with the use of volatile agents, since the company in its submission mentioned the side effects associated whit IV sedatives.
One expert: There are lots of side effects and they are listed in the product literature. But they are relate to the volatile compound itself not the device itself.
Another expert agreed that there are various side effects of the medication, but it is important to also consider device related adverse events. Thy noted that there is more endotracheal tube blockage with AnaConDa compared with using a heated humidifier. This can be frustrating and impacts on the use of the device.
A further expert suggested that this is an issue with all heat and moisture exchangers (HMEs) and not just with AnaConDa. They highlighted that fluoride accumulation can result from over 24h use of Sevoflurane use leading to kidney injury, but that fluoride accumulation is generally not measured in practice. There is variability in clinical opinion as to how problematic this is in practice, but potential symptoms include polyuria and diabetes insipidus. But there is a potential drive to move away from Sevoflurane use anyway in patients requiring over 24h sedation.
One more expert noted that 15-16 years ago, they tried to measure fluoride levels in their paediatric patients but this was unwieldly. They noted that there is a risk of vasodilation and cardiovascular impact with volatile sedatives, and when used in patients with raised intracranial pressure, there will be a predictable drop in cerebral perfusion pressure (due to the cardiovascular impact). There is also a risk of withdrawal phenomena, but this applies to all sedatives. They also note that in their paediatric patients there have been temporary neurological changes (in particular, fixed or oval pupils) that lead to unwarranted CT scans to investigate whether they have been caused by cerebrovascular events. Other temporary side effects include clonus, especially lower limb clonus.

8. The 2014 Intensive Care society guideline on sedation in ICU mentions notes
   'Difficulties in delivery and scavenging combined with concerns over fluoride accumulation and the dependency with ventilation limit the use of volatile anaesthetic agents on the ICU.'
   Do these concerns relate to the use of AnaConDa in relation to?
   a. Fluoride accumulation
   b. Dependency with ventilation (what is the meaning of this)

The EAC wanted to clarify the meaning of these as the referenced document is the closest document to a sedation guideline in the UK.

- *Point a. has been covered under question 7*

One expert explained 'dependency with ventilation' refers to the need to have a reliable minute ventilation to be able to deliver the drug to the patient.

General Question

9. The EAC asked about the regulatory status of volatile compounds for sedation vs anaesthesia.

The conclusion of a brief discussion regarding the regulatory status of volatile anaesthetics was that they are not licensed for patient sedation in ICU.

One expert stated that conceptually there is little difference between anaesthesia and sedation, and these should be understood as a continuum of the same intervention.
Another expert agreed that clinically it is a continuum, but licensing wise these are two different interventions. They noted that volatile agents are not licensed for sedation in the UK and are administered via a local approval process.

Appendix 3: Additional notes sent by one of the clinical experts on the issues discussed during the expert engagement meeting

Questions for discussion

Population

1. Considering paediatric populations
   1. Do you use the AnaConDa-S in children? No. But 50ml device in standard configuration safe for kids >30kg based upon minimum safe Vt of 200ml and Vt of 6ml/kg IBW.
   2. If so, under what circumstances would you use it? Status asthmaticus / problematic sedation / limited IV access
   3. How would use in children differ from adults? None in principle.
2. Considering patients with opioid dependency
   1. What would your procedure be for use with opioid dependant patients? a. very rare problem b. no evidence to support rapid / ultra-rapid detox protocols c. volatile use would mimic propofol / midazolam use in this patient group. What prompted this question?
   2. Would opioid dependency be a contraindication for use? No
   3. What is the proportion of patients with opioid dependency that are treated in an ICU? Problematic opioid dependency, very low.
3. Considering pregnant women
   1. Would you consider the use of volatile anaesthetics as an absolute contraindication in this patient group due to potential teratogenic effects? No. Isofluarane > sevoflurane risk but both low. Hence, risk : benefit comes into play. Probably never a first line sedation option, so of limited concern.
4. Any patient groups in which you would avoid using AnaConDa/volatile sedation. Patients with a history of malignant hyperthermia. see https://anaesthetists.org/Home/Resources-publications/Guidelines/Malignant-hyperthermia-2020
5. Any patient groups for which you would particularly prefer to use AnaConDa over IV sedation? Status asthmaticus / problematic IV sedation / possibly ARDS (at high risk and with) / adjunctive in refractory status epilepticus /

Device

6. How often would you use the alternative placement of the AnaConDa device (can you comment if this proportion of patients would be different in the adult and paediatric populations)? Very rarely and **ONLY** if hypercarbia problematic ***AND*** risk : benefit of volatiles favoured continuation.
7. Who is responsible for the device set-up (doctor, bedside nurse, nurse technologist, healthcare scientist/technician)? Institution specific.
8. Is there any special governance associated with AnaConDa use that would not be required for IV sedation. Yes, environment monitoring and active symptom surveillance. Given environmental impact, second-line option hence review of appropriate use. Risks management associated with less frequently used technologies.
9. For the sedative level monitoring do you use side-stream or main-stream gas monitoring?
10. Do you use FlurAbsorb with the AnaConDa or do you utilise an active scavenging system?

Sedation

11. How long, on average, would you estimate sedation be needed for a mechanically ventilated patient? Depends upon the patient, the acute pathology, its evolution, and the clinical course e.g. complications
12. What RASS score is generally aimed for during sedation? -2 to +1
13. What RASS score is generally achieved during sedation? -2 to +1
14. With respect to the two previous points, would sedation depth differ with the length of sedation, i.e. does sedation tend to be deeper in earlier phases of ICU stay vs later. Should always be titrated to individual patient and goals of sedation
15. Do you ever use an anaesthetic machine to deliver sedation on your ICU. Only if there is no alternative e.g. during COVID pandemic
16. What would you consider the standard of care to be for ICU sedation in adults and children? PADIS https://journals.lww.com/ccmjournal/Fulltext/2018/09000/Clinical_Practice_Guidelines_for_the_Prevention.29.aspx
17. Do you tend to used Isoflurane or Sevoflurane.. What would be the typical (range and average) rates at which these are administered be.
18. Are there any issues associated with the use of AnaConDa in ICU patients also requiring pharmacological paralysis? None
19. What is the regulatory status of the use of volatile anaesthesia in the paediatric intensive care population? Unknown

Other

20. Do both isoflurane and sevoflurane have bronchodilatory effects? Yes; conflicting data regarding equipotency.

21. Are there any iatrogenic effects associated with sevoflurane or isoflurane? Nausea / vomiting + dizziness + headache + delirium + chronic cognitive dysfunction + eleptogenic at high MAC (sevoflurane only); hypotension [vasodilation and blunted autonomic response]; respiratory drive depression; low grade (repairable) DNA damage; depress neutrophil function;

22. The 2014 Intensive Care society guideline on sedation in ICU mentions notes
'Difficulties in delivery and scavenging combined with concerns over fluoride accumulation and the dependency with ventilation limit the use of volatile anaesthetic agents on the ICU.'
Could you comment on both of these later points, including if these concerns relate to both volatile agents or just one, and if these concerns as such also relate to the use of AnaConDa?

1. Fluoride accumulation. Clearly established as not of concern
2. Dependency with ventilation (what is the meaning of this) Patients with critically elevated ICP ***AND*** challenging ventilation / CO2 clearance = contra-indication, otherwise not an issue; merely requires attention to detail.

Appendix 4: Responses from 7 clinical experts regarding the prioritisation of outcome measures

Would you please be so kind and list the top 5 outcomes listed in the outcome section of the scope that you would consider most important if you would be making a clinical decision on whether to use the AnaConDa on a patient or not? For outcomes that have several different measures listed (e.g. 'psychological outcomes') please list the one preferred measure (e.g. 'PTSD' or 'memories of hallucination' but not both).

Expert 1	Expert 2	Expert 3	Expert 4
1. Reliable, sustainable sedation efficacy 2. Effective sedation in patients with life-threatening bronchospasm and asthma (although I would stress that in this scenario, the bronchodilation effect is the key outcome) 3. Shorter, more predictable wake up time after ICU sedation and avoidance of slow sedative excretion and slow emergence from sedation 4. Shorter duration of mechanical ventilation and increased ventilator-free days 5. Reduced costs compared with IV sedation	IN order from the list # The outcome measures to consider include: * *wake-up time after ICU sedation* * *sedation efficacy (time to extubating, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale)* * *Effectiveness of ventilation on people with bronchoconstriction* * *duration of mechanical ventilation/ increased ventilator-free* *days*	These are the five I would focus on. This is partly a pragmatic decision based not only on what I think is most important but also what I think Is most feasible to demonstrate. Please note that device related adverse eventsa should probably be device / volatile anaesthetic drug related adverse events. • wake-up time after ICU sedation • sedation efficacy (proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale)	1. A second-line sedative intervention for mechanically ventilated ICU patients, intolerant of and / or suboptimally managed with conventional continuous IV sedation regimes. Advantages include a more reliable / predictable response: rapid onset and comparatively rapid offset - for neurological assessment; POSSIBLE organ protection of lungs / brain / heart. Disadvantages include risk of environmental contamination affecting healthcare workers, other patients and visitors; POSSIBLE reversible DNA damage see - DOI: 10.1007/s10877-017-0077-0 AND https://pubmed.ncbi.nlm.nih.gov/21595613/ ; environmental / atmospheric damage. 2. Early rescue or even first-line sedative in patients with refractory status astmaticus requiring mechanical ventilation. 3. Late / rescue intervention in super-refractory status epilepticus

I would just add that in our unit 'Reduced dependence on intravenous access' would be an important outcome, and would probably appear at number 3 in the list	* *Device-related adverse events.*	• oxygenation and inflammatory markers in patients with ARDS • duration of mechanical ventilation/ increased ventilator-free days • Device-related adverse events.	4. POSSIBLE second-line intervention to prevent or manage early ARDS 5. AWAITING TRIAL EVIDENCE - primary intervention to improve short, medium and long term neurological outcome benefit in patients post cardiac surgery / post cardiac arrest / "others"

Expert 5	Expert 6	Exper7
- Effectiveness of ventilation on people with bronchosconstriction - Cognitive recovery - duration of mechanical ventilation/ increased ventilator-free days - sedation efficacy - wake up time after ICU sedation	As I highlighted in the engagement meeting - my experience as a trainee of using volatiles in intensive care is as a rescue strategy in bronchospasm, and specifically asthma, rather than routine sedation. This would be the case in most hospitals across the North-West of England. I am therefore approaching this from a different angle to the other experts on the panel as they seemed to be using the device for routine sedation on intensive care. This makes my feelings on outcomes likely to be somewhat different as they are dependent on the context in which the device would be used in the trusts I have worked. My top 5 outcomes when using/considering this device in my current hospital placements would be as follows: 1. Effectiveness of ventilation on people with bronchoconstriction 2. Reduction of additional bronchodilators 3. Sedation effectiveness in patients with life-threatening bronchospasm and asthma	Top five outcome measures I think there is still some confusion as to the difference between using volatile anaesthetic agents for sedation per se and for treatment fo bronchodilation. We need to be explicit in terms of whether this NICE review is around sedation per se or treatment for bronchospasm. At the moment, this reads in a way that suggests there is confusion in the minds of the authors between the two, which unfortunately negates the clinical acceptance of the document. sorry to be so explicit .. in terms of outcome measures in critical care • wake-up time after ICU sedation - this really only applies / is useful in anaesthesia • cognitive recovery - I would suggest this is very hard to determine in criticla care with many confounding factors • sedation efficacy (~~time to extubating~~, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale) - probably usefu • markers of cardiac injury, liver, gut, kidneys and brain for short-term operative sedation - short term operative sedation, this does not apply to critical care, volatile anaesthetic agents arent used for sedation for operation, they are used for anaesthesia • sedation effectiveness in patients with life-threatening bronchospasm and asthma - possibly useful

	4. Wake-up time after ICU sedation 5. Duration of mechanical ventilation/ increased ventilator-free days	• oxygenation and inflammatory markers in patients with ARDS - there are too may confounding factors here to use these as outcome markers • psychological outcomes (e.g. memories of hallucination, and long-term psychological morbidity, PTSD) - useful to compare to standard sedation regiemes, Propofol plus opiate in adults • Effectiveness of ventilation on people with bronchoconstriction - possibly, difficult to measure • Reduction of additional bronchodilators - perhaps • duration of mechanical ventilation/ increased ventilator-free days - too many confounders • length of stay in the ICU.too many confounders • hospital length of stay/ hospital-free days.too many confounders • Amount of volatile anaesthetic agent used - this is not an outcome measure • Staff exposure to volatile anaesthetic agents - how would you measure this ? • Staff time in the ICU - not sure what this means • Amount of opioid drug used - maybe, but there is then the so what question • Device-related adverse events. - if they are defined, perhaps Sorry, fairly negative replies, I think this relates to there being confusion still as the the difference between the use fo volatile anaesthetic agents in critical care for treatment and sedation (they are different) and then the impact of the device itself, I think they all need to be separated out otherwise this confusion continues

Appendix 5: Responses from 4 clinical experts regarding presenting the data according to certain subgroups

We have a lot of evidence from papers looking at cardiac surgery patients. This is not a subgroup specified in the scope. As such, would you still find it beneficial to have these studies discussed as a separate group? Would you find having separate discussions on the evidence for long-term sedated patients and a sperate discussion on the evidence for short term sedated patients sensible? Would you consider post-cardiac surgery patients generally a representative group for short-term sedated patients?

Expert 1	Expert 2	Expert 3	Expert 4
Again - I have limited experience, but on our cardiac POCCU, the vast majority of elective patients are extubated within 24 hours post op and would therefore represent a short term sedated patient. We do not use volatiles anaesthetics in this patient group in the centre I work at currently.	We have a lot of evidence from papers looking at cardiac surgery patients. This is not a subgroup specified in the scope. As such, would you still find it beneficial to have these studies discussed as a separate group? Cardiac Surgery patients are a very discrete, elective on the whole group of patients who aren't representative of the general critical care population. If the evidence is presented, it must be done so in this context. I suppose it is reasonable to use this group / evidence from this group to indicate safety in short term, post-operative sedation on critical care, it does not automatically translate into safety in the wider adult critical care population. Would you find having separate discussions on the evidence for long-term sedated patients and a sperate discussion on the evidence for short term sedated patients sensible?	I would recommend including cardiac surgery as a separate group. I would suggest you keep cardiac separate from general 'short term sedation' as the cardiac issues ca be quite specific and I believe that some of the literature relates specifically to markers of cardiac injury / cardiac protection (ie. troponin), based on the recognised benefits of volatile anaesthetics for 'pre-conditioning'. Where the cardiac literature relates to other process or outcome metrics such as time to wakening, duration of ventilation, then there will be some overlap with other short term sedation' groups. *This expert was asked an additional follow-up question 'The problem is then that if we separate this group out, this might suggest that between group differences in the other outcomes (e.g. as you mentioned: ventilation time or*	I am not an expert in Cardiac …, but I do think it should be a different scope from the ICU use of inhaled sedation

	Given the comments I've made above, I think this would be necessary, again though are we looking at the safety of the Annaconda device or isoflurane, or both in combination ? You also need to be fairly explicit in terms of defining short and long term sedation Would you consider post-cardiac surgery patients generally a representative group for short-term sedated patients? No. They are a specific patient population,	*wake-up time) will then be perceived to only apply to this group. So perhaps to phrase my question differently: do you think that evidence on non-cardiac specific outcomes from the post-cardiac surgery group would be generalisable to other groups and if yes, then to which?' [no answer was provided]*	

Appendix 6: Notes from Company Post Economic Submission Meeting for MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

This document summarises the discussions that took place at the company post economic submission meeting for MT582 AnaConDa-S, which took place on Friday 04th June 2021, 1:00 - 2:30pm. Written responses were supplied by the company in advance of the meeting on 4th June 2021.

Agenda

1. **Welcome and introductions**
2. **EAC clinical evidence review**
3. **Discussion about the issues raised in the clinical evidence review**
4. **Questions on the economic evidence submission**
5. **Next steps**

NICE
Kimberley Carter, Health Technology Assessment Adviser
Federica Ciamponi, Health Technology Assessment Analyst
EAC
Rhys Morris, Cedar Directors
Michal Pruski, Researcher
Laura Knight, Senior Researcher
Susan O'Connell, Senior researcher
Company Attendees
Peter Sackey, Chief Medical Officer
Per Svangren, Consultant for Sedana
Paul Miller, Consultant for Sedana
Jens Lindberg, Vice President Commercial Operations
Christian Malin, Country Manager

Themes discussed:
EAC clinical evidence review

SED001 Study

Comparison with Midazolam using Krannich 2017
Outcomes
What are the inclusion criteria for SED001
Difference in time to extubation depending on reason for ventilation
Adverse Events
Model Query
Confidential Data
Additional Discussion

EAC clinical evidence review

The EAC briefly discussed which studies from the company's submission they have included in their evidence review, which they have excluded and also noted any additional studies that they have included that were not included in the company's submission. The EAC noted that it excluded all the studies that did not use AnaConDa as the intervention as well as one study that, though using the AnaConDa, focused on bispectral monitoring. The company noted no objections to these exclusions, highlighting that they were expecting the non-AnaConDa studies to be excluded.
The company asked whether the EAC has restricted its inclusions to randomise controlled trials (RCTs). The EAC noted that they did restrict the evidence to comparative trials but not to only RCTs. The company noted that this would explain the discrepancies and had no further comments on this issue.

EAC Questions for Company on Economic Submission

SED001 Study

1. Would the company be able to share the full trial report with the EAC/NICE for reference?

The company provided the full trial report and further analysis to the EAC. During the meeting there was a discussion around the availability of the data in the public domain and it was established that for now the results should remain AiC but it was noted that the journal publication is currently in the review stage and will likely publish before the end of the process. If this is the case, it was agreed that the EAC and NICE would revisit the need for results to remain confidential.

2. Duration of mechanical ventilation: The two models use different measures of duration (mean and median). Do the company have the median duration of mechanical ventilation for the SED001 study?

The company provided means and medians for the SED001 trial for different population subgroups with references to where these could be found in the trial report. The company noted that the published Krannich study reported only medians and offered to contact the authors if it was required. The EAC noted during that the meeting that mean values were preferable and the request for medians was simply to compare 'like with like' if necessary. It was agreed that the EAC would contact the authors of the study if necessary.

3. In the company clinical submission, analysis of SED001 has been done in a number of ways including all patients, analysis excluding switches, analysis excluding deaths.
    a. Can we clarify what patients are included in each analysis group and discuss the rationale for these subgroup analyses?
    b. Are all subgroup analyses post-hoc?
    c. Can the company provide any information on the deaths during the study?

The company provided references to where this information could be found in the economic submission and the trial report.
The company noted that a total of [redacted] were included in SED001, complete data on [redacted]*. A pre-specified analysis compared 30day data by randomised group allocation (for the 48+/-6h randomised study period), although the protocol specified that after 48+/-6h the sedation could continue according to local practice as deemed necessary by the treating physician. A total of [redacted] switched sedation regimen [redacted] at some point post randomised study period and before 30day follow-up. The post-hoc analysis excludes these [redacted] who switched sedation regimen, in order to control for cross-over and includes a total of [redacted], the non-switchers.
Deaths are described in CSR section 12.4 (page 174). For the non-switchers all available data were analysed to show ICU and ventilator duration, an additional analysis excluded the [redacted]
During the meeting the company confirmed that the base case analysis is the non-switchers because this is more relevant to the decision problem and that they did not do anything too complicated in the cost-consequence model. The company though noted that non-switcher analysis was a post-hoc analysis and that duration of ICU stay was not a pre-specified outcome.
The EAC queried whether the study had collected any information on why patients sedation may have switched after the randomisation period. The company noted that this was likely a combination of factors such as cost and German regulations (where the study was conducted), and physician discretion. Inclusion criteria for the study required that that units had to have mastered the method of the inhaled sedation with AnaConDa and this may have had an impact on the decision.
The company noted that the trial only required randomised sedation method be employed for 48hours from randomisation and that after this period they company were careful not to influence the decisions to change sedation method. It was left to the individual clinicians to make the decision however the company noted that the top recruiter in the study stayed with whichever sedation (IV or inhaled) once started.

Comparison with Midazolam using Krannich 2017

4. Could the company comment on the rationale for choosing this particular study for the second scenario?

In written responses the company noted that SED001 is an RCT comparing directly versus propofol. Krannich et al. 2017 provides clinical data from a routine clinical practice (non-RCT) setting with an alternative IV sedation comparator (midazolam).
The clinical SLR considered all available clinical studies directly comparing IV sedation and inhaled sedation in this setting. Krannich et al. 2017, although not an RCT, was the largest

observational study comparing IV midazolam sedation versus inhaled sedation in this setting. The company noted that Krannich et al. 2017 provides a different perspective on the decision problem with respect to both study design and the comparator used.

Outcomes

5. Could the company comment on the outcomes 'Duration of mechanical ventilation', 'time to extubation' and whether/how these are different outcomes?
6. For clarity, is the outcome 'duration of mechanical ventilation' relevant only to calculate the cost of sedation per patient?
7. To what extent is the duration of mechanical ventilation impacted by the reason for ventilation?

The company provided written responses and noted some references which may be of use to answering these queries.

The company noted that extubation and indeed re-intubation may occur during the clinical management of a patient in ICU during the period that mechanical ventilation in required, though there is little data on re-intubation risk. Duration of mechanical ventilation refers to the time that the patient has been treated with mechanical ventilation. A patient normally requires sedation during the period of mechanical ventilation.

The duration of ventilation is not only relevant for cost calculations (though together with length of ICU stay it is the main driver of cost), but also of clinical value to the patient's overall outcome to have a short as possible time on mechanical ventilation. This is true for cognitive as well as somatic outcome measures.

The reason for mechanical ventilation may be respiratory or non-respiratory. The different diseases in these sub-groups have strong impact as well. A patient with acute brain injury might need long term ventilatory support because the patient's respiratory drive is insufficient, or the airway is not protected. A patient with a post-operative septicaemia might need long support due to high pressure in the abdomen and multiorgan failure with need for deep sedation and a third patient with a pneumonia might need long support due to poor oxygenation or acute respiratory distress syndrome. The severity of the respective disease is thus important for the time spent on the ventilator, but also the sedative and analgesia management, as has been demonstrated in numerous studies.

e.g.

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation | NEJM;

Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial - PubMed (nih.gov);

Sequential use of midazolam and propofol for long-term sedation in postoperative mechanically ventilated patients - PubMed (nih.gov)

A follow-up question to add more clarity from the EAC related to how these outcomes are reported in the published literature comparing IV and inhaled sedation established that:

Time to extubation is the time from stopping the sedative drug to being able to remove tracheal tube (hours, mins generally)

The EAC noted that one study did report time from sedation to readiness to extubation which is different.
Duration of mechanical ventilation is usually time from randomisation or possibly some time prior to randomisation or some equivalent. It is the total period of time for mechanical ventilation including the time to extubation.

Although this added important clarity, the EAC still had a query around time to extubation vs extubation time? It was agreed that the EAC would check the details in the published literature and follow up with the company on e-mail if necessary.
The company noted that the reason time to extubation is an important outcome is because a shorter extubation time is valuable to patient and staff (resource etc, clinical) and that if the time on the ventilator and time spent in ICU can be impacted then this will have positive cost impacts.
The company noted in the written responses that the reason for mechanical ventilation will have an impact on the reason. During the meeting the company further clarified with examples including:

- COVID patients going to be ventilated for much longer with patients who are unconscious due to intoxication for example
- Healthy patients being sedated may need shorter ventilation times compared to a patient with underlying health conditions (e.g. COPD)
- The way you sedate matters too: Daily stopping times with IV sedation can have an impact, light sedation versus heavy sedation.
- Daily assessment of patient and patient needs such as anaelgesic requirements can shorten time on ventilation.
- Awareness of when to stop the drugs? Are we good enough at knowing/understanding this?

The EAC had some follow-up questions

What are the inclusion criteria for SED001
The company noted that the inclusion criteria for the SED001 study are listed in the draft study report. Briefly, the SED001 trial's inclusion criterion was being ventilated for 24h with a tidal volume sufficiently big for the AnaConDa 100ml dead space not to be a counterindication, though severely patients were excluded. This was a very different population than that of the retrospective study carried out by Krannich et al. (2017), where the patients were post cardiac-arrest receiving therapeutic temperature management. These patients are cooled to try and protect brain function but these patients need deep sedation to prevent shivering. The patient cooling was meant to achieve a lower metabolism to save as many neurons as possible, though this reduced metabolism could also increase the chances of sedative accumulation. In Krannich patient needed to be at -4/-5 RASS whereas in SED001 patients had to be sedated to a [redacted]

Difference in time to extubation depending on reason for ventilation
It was further noted by the company that depending on how you sedate patients and what their background condition is, this can affect the time to extubation. Patients with problems that well affect sedative metabolism and clearance, such as those with liver conditions and multi-organ

failure, will take longer to reach extubation criteria such as reaching a Glasgow Comma Scale score of 8, which will indicate that they can maintain their own airway, as well as adequate pulmonary function. This is because the drug will take longer to metabolise as well as it will take longer for any active metabolites to be excreted, even after drug administration has been stopped. This well document with IV sedation but there is not much data regarding this phenomenon with respect to AnaConDa delivered sedation. Similarly, patients with neurological injuries and the elderly might be very sensitive to the sedative agents, which can also affect wake-up time.

Adverse Events

8. Adverse events are not included in the model, is this because there are no adverse events considered to be specific to inhaled or IV sedation?

The cost-consequence model made the following simplifying assumptions:

Assumption	Justification	Source
Sedation efficacy, tolerability and safety are **not** different by sedation strategy (isoflurane via AnaConDa vs. IV SoC sedation)	SED001 demonstrated non-inferiority. Clinical SLR found no evidence to support differences in these metrics.	SED001 RCT, clinical SLR (part 1 submission)
Sedation costs, monitoring and administration do differ by sedation strategy (isoflurane via AnaConDa vs. IV SoC sedation)	Although there are only small differences in sedation drug costs device/ equipment/ consumables costs are clearly different by sedation strategy. Dose renewal (drug administration) will be much more frequent with IV sedation than inhaled isoflurane. Daily sedation interruption protocols are much more likely with IV sedation in order to avoid accumulation.	UK Clinical KoL validation

Our rationale for this is empirical, in section 6 of our NICE clinical submission (part 1) we detail the AEs from SED001 and 13 RCTs from the SLR.
For the cost consequence model there is nothing consistent in the evidence to suggest that there are any adverse events which would impact the model.
Numerically more adverse events for isoflourane – hypertension and agitation related to the rapid clearance of the drug but these were not considered for inclusion as they are not serious adverse events or device specific adverse events and occurred after stopping sedation.

Model Query

9. The sensitivity analysis doesn't appear to be functional, is there a version with results and sensitivity as reported in the submission?

The company provided the sensitivity analysis details for the model.

Confidential data

10. To what extent are the cost data for AnaConDa commercial in confidence? (Table 5, resource use costs have nothing redacted, is this because it is a total derived from individual costs that are CiC?).

Sedana price list is CiC however NICE need to publish a price for the technology and there was a discussion around what version of the price should be used?
It was agreed that NICE would work with the company on this, with the company noting that perhaps some derived value could be used. The EAC also asked the company to provide a list of all embedded documents in their submission to ensure that no confidential information from them gets released.

Additional Discussion

The company queried how long the EAC's report usually is. The EAC noted that the length of the report depends on the volume of evidence available.

Appendix 7: Responses from 5 clinical experts on some issues relating to drug dosages and AnaConDa set-up

1. What would be the most likely dose of propofol used during IV sedation? BNF has a range from 0.3 to 4mg/hour which is quite a wide range so a rough estimate for an average IV sedation would be helpful.
2. What would you consider to be an appropriate average patient weight from which to calculate an average dose?
3. Are there any additional drugs that would be included with IV propofol that wouldn't be relevant for inhaled isoflurane?
4. Similarly, are there any additional drugs that would be given with isoflurane or sevoflurane
5. With midazolam, is this always given with Fentanyl (or other opioid)?
6. I appreciate that in the UK midazolam may primarily be used for children,
    a. in this setting can you provide an estimate of the doses that would be used?
    b. how would the dose differ for different age groups (very young children/babies and older children)?
7. Are there any training requirements for moving from IV sedation to inhaled sedation methods?
8. Considering long versus short term sedation is there anything specific should we be aware of?
    a. Is there a rough estimate of what is considered long term and what is short-term? (days or hours of sedation)?
    b. Would the choice of sedation method (IV or inhaled) be influenced in any way by whether a patient may need long or short-term sedation?
9. One publication talks about deaths avoided with inhaled sedation,
    a. can you comment on whether you think deaths avoided is a reasonable outcome to consider?
    b. Are you aware of any specific literature that addresses this outcome?
10. With regards to AnaConDa set-up in your centre:
    a. Are all ICU nurses trained to take care of patients managed with the help of AnaConDa?
    b. Who in your centre is trained to do the initial set-up of the AnaConDa on a patient?
    c. Do you know what NHS band they usually are?
    d. Do you know how long does it usually take them to do it from arriving at the bedside)?

(Just for context: in some centres while any nurse will be able to care for a patient with AnaConDa only some people will be trained to do the initial set-up. Some places utilise healthcare scientists/technologists to do this, while some have dedicated nurses. We need to understand staff involvement in the use of the device and how it would compare with standard of care).

Expert 1	Expert 2
1. This is very dependant on the individual patients … average likely to be around 150mg/hour. I think your scale was mg/kg/hour …. 2. 70kg – but all our patients are weighed on their beds in the unit. 3. Not any others that we haven't already mentioned 4. Not in the first istance 5. Yes – in adults 6. *(no answer given)* 7. Yes. The use of the volatile system will be needed / uses of inhalational anaesthesia etc 8. A) Over 5 days – I think is long term .. B) Not in our unit 9. A) Not ebough data for this for volatile anaesthesia in ICU B) (no answer given) 10. A) Yes – but we have been using it since August 2019 B) All the nurses … Sister is the oversight C) 5 Staff Nurse and 6 for Sister D) 5 mins – less than 2 mins if the AnaConDa is pre-prepared …	1. Dose is titrated to desired effect i.e. lowest dose to achieve desired level of sedation. Prolonged [hours to days] exposure to higher doses [adults >200mg/hour] runs the risk of complications [in order or prevalence] hypertriglyceridaemia, pancreatitis, propofol infusion syndrome. 2. Apologies, I don't understand the question. Body composition is more of an issue with lipophilic drugs - this includes propofol and inhalational agents. 3. Both would require adjunctive analgesics, usually sedative opioids. 4. Verses propofol, the only theoretical issue is that propofol has anti-emetic properties whereas inhalational agents are pro-emetic. Probably not an issue in the real world. 5. As stated in 3., sedative analgesics are a mainstay [fentanyl / alfentanil / remifentanil] and some would advocate these a single / first agents with adjunctive sedatives only if required - see, for example, http://www.ncbi.nlm.nih.gov/pubmed/27075762 6. this is worldwide not UK specific A) (*no answer given)* B) I defer to Paediatric colleagues for this 7. Yes. The vast majority of ICU nurses have no experience of inhalational anaesthetics, which require some subtle but important changes in thinking and approach. 8. A) Arbitrarily "short-term" is hours to 1-2 days max. B) The agent is less important than how well it is used and the patient

	population being considered. A number of “short-term” randomised comparator studies are underway e.g. post cardiac surgery 9. A) No, very poor outcome measure. B) No, not least as this measure is poor for this question 10. A) This is unit specific and depends upon a number of variables B) As above C) As above D) As above *This expert was asked to provide more information on question 10 to reflect their local practice. [The information was not provided].*

Expert 3	Expert 4	Expert 5
1. Dose range varies significantly to be honest. 2. adult 85kg ? 3. usually given with an opiate 4. may include an opiate 5. usually *6. (No answer given)* 7. Yes, understanding of dosing regimes, set up, risks, complications etc 8. accumulation of fluoride A) Not by definitiation, suggest short term 24 hours B) probably not 9. A) no it isnt, cause of death on ICU is heterogenous, whilst a specific outcome it has many influencing factors B) (*No answer given)* 10. A) no, depends on local preference and usage B) nursing staff C) band 5/6 D) no idea sorry, but likely to be less than 30 mins if everything easily available	1. The maximum dose of propofol should be 4mg/kg/hour to avoid propofol infusion syndrome 2. Most of the time in ITU we use ideal body weight or lean body weight for this type of calculation 3. This is very difficult to comment on as the sedatives given with propofol often depend on the context and patient they are used in 4. An opiate 5. Usually yes 6. Not too much experience with this but it is dosed based on weight 7. Yes - junior trainees may not have done anaesthetics prior to ITU and have little experience with volatile anaesthetics. Similarly with nursing staff in our region - we rarely use volatile agents on intensive care and therefore would need training to ensure staff are comfortable and confident in using this. 8. Long term in ICU I would consider days to weeks. Hours of sedation tends to be more	1. That dose rage is right and does reflect practice. 'Average' is prob 1-2mg/kg/hr 2. In practice we use the patients weight, but if talking about 'averages' for example to estimate typical costs, base it on 70kg 3. No. More likely to use multiple agents with PPF, but because volatiles more potent can usually get away with just volatile +/- low dose opiod 4. +/- low dose opiod (fent / alfent) 5. Usually, can never say 'always' 6. N/A for me 7. Yes, need a governance process s- guideline, device training etc 8. A) Don't know if there are agreed definitions but to me short term is <24hrs, long term > 72hrs, 24-72 somewhere in themiddle B) Possibly. IsonConDa study focused on short term. Sevoflurane may be problematic > 72hrs due to Fluroide accumulation. However, benefits of volatile (Iso) may accrue over time as the issue of drug accumulation is not there 9. A) I don't think so. I don't think the data is good enough at present to suggest a mortality reduction from volatile in my opinion. To the best of my knowledge I don't think any trial of different sedative regimes (two different drugs as opposed to two different approaches ie. daily sedation interruption versus standard) is a/w dec mortality. I can see an argument for how it might be plausible, but

	common in post-operative critical care than general intensive care. 9. I imagine this relates to bronchospasm in asthmatics and using volatile anaesthetics as part of treatment of the condition as well as sedation 10. We do not routinely use this device for sedation in my current centre or anywhere else in our region (North-West)	demonstrating it is practice likely to be exceptionally difficult / impossible. B) No 10. A) No, selected senior nurses only B) Our ECMO Cliical urse specialists + now just trained our senior band 7 group + technicians do technical set up – joint nursing / tech set up C) 7, hoping to extend to B6 shift managers too D) 10-15mins

Appendix 8: Company response to a set of regarding staff training and cost values they have used

Training

- Does the company provide any training?
- If so, is there a cost to the training?
- How long does the training take?
- What staff normally attend training (nurses, consultants, technologists etc)?
- Is the training specific to incorporating the AnaConDa device into an inhaled sedation system or do you provide training on setting up a complete inhaled sedation system using the AnaConDa device? In other words, do you just provide training on how to set-up and manage the AnaConDa device or do you also provide training how to manage a patient on volatile sedation?

Sedana Medical provided the numbered list of points below on the training they provide. This is all support provided by the company with no costs. NHS staff time allocated to this is professional development training and CPD accredited.

1. Fully CPD accredited E learning which takes an hour to complete and has Q&A
2. Face to face classroom sessions over 3 separate days for a hospital where we deliver 4 -5 1 hr sessions on "WHY" are you looking to use AnaConDa what does the research say which patient groups Side effects contraindications and "HOW" where we demonstrate how the AnaConDa works with an intubated dummy patient and a ventilator syringe pump and gas monitor set up so we can replicate the process. Certificate and CPD accreditation awarded (1 hr). This is delivered to as many staff as available over the sessions over 4 days, with a specific emphasis on all the Practice development nurses and the Shift Leads which means going forward there will always be someone on duty who has been trained to use the AnaConDa.
3. "GO LIVE WEEK" we agree a start date with the unit following the classroom sessions where they commit to put all suitable mechanically ventilated patients who require sedation onto the AnaConDa and we support them for that week training by the bed side for both shifts. (also certificated and CPD accredited)
4. We present on the Induction course for new ICU nurses.
5. We present on the equipment training update days.
6. As well as nurses we offer tailored sessions to Physios therapist which cover things they need to know and Pharmacokinetic / Pharmacodynamic session for the pharmacists, training for all medical staff and technicians.
7. There are a large number of educational webinars on the Sedana medical website. The UK webinar from November has an RCOA accreditation.
8. We provide 1 page study summaries of relevant material and latest research.
9. We provide a number of generic SOP for them to adapt to their units specific requirements
10. We connect units with other ITU's who are using the AnaConDa for peer to peer support.

11. For New Hospital we offer a 1 hr session over TEAMS with a consultant who has been using the AnaConDa for over 2 years and he talks about his experience ,challenges of introducing the therapy and types of patient groups he uses it on

    In addition to this we provide them with user manuals which take you through every step of how to set the AnaConDa up. We provide a link onto their computers which takes them to the set-up video's for reference (with permission). We provide QR code stickers to place on the ventilators so they can access the website and training via their mobile phone.

    We are in the final sign off for a competency assessment test for hospitals to use so they can keep a log of the nurses training and competence. This will be embedded into the E-Learning shortly.

Cost of Propofol

- What was the reason for using the eMIT rather than BNF for the propofol costs

Both sources are fine of course, we have no strong preference either way. We chose to use this source: Drugs and pharmaceutical electronic market information tool (eMIT) - GOV.UK (www.gov.uk)
For generic drugs, eMIT may better represent the prices actually paid – since it presents the average price paid for that product over the last 4 months of the period. It also shows NHS hospital-sector annual usage from English trusts.

- Can you give a little more detail on where the cost for the infusion syringe came from – is this just an assumption or is there a source/validation from a clinical expert?

The inclusion of costs for more frequent dose renewal and the need for DSI came from discussion with clinical experts (we report in the clinical validation section). The number of infusion syringes per day (24h) is calculated based on dose/ vials per hour rate. We assign a cost of £1 per syringe for supply and disposal as a conservative estimate. The BNF lists a range of propofol products including pre-filled syringes, but these are higher cost. The syringe for AnaConDa is priced at [redacted]

- Similarly for the cost of nurse time – is there a source for the £20 nurse time cost?

We assumed the £20 per hour as a conservative allocation of costs here. We looked at PSSRU hospital-based nurse costs (Unit Costs of Health and Social Care 2020 (pssru.ac.uk)). Again, we were aiming to be conservative with our costings, so we have only included annual salary costs (not overheads, capital costs assigned etc.). For a Band 6 Nurse, with salary circa £34,000 and working 1,573 hours p.a the hourly rate is a little above £20 per hour.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from CEDAR to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies, you must inform NICE by 12pm, **30 June 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

24 June 2021

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 6, final paragraph: EAC defines sedation using AnaConDa as a 'dominant strategy' – clinical benefits AND cost saving. Hence, it would be accurate to state the conclusion is a dominant strategy.	"The conclusion of the EAC is that, compared with IV sedation, there are clear clinical benefits associated volatile sedation delivered using the AnaConDa device and using the AnaConDa device to deliver inhaled sedation is cost-saving due to a shorter duration of ICU stay. Sedation using AnaConDa is a dominant strategy compared to IV."	Clinical benefits and cost saving compared to IV comparator means sedation using AnaConDa is a 'dominant strategy'. The term 'dominant strategy' is very important in HTA decision-making.	(N*ote for all issues: page numbers vary between the company and EAC versions of the report due to presence/absence of the coversheet*) Thank you for your comment. The EAC has avoided using the phrase 'dominant strategy' as this has a particular meaning within health economic analysis and is related more commonly associated with cost effectiveness planes and ICERs. The EAC has not made the requested changes to the executive summary, but made minor edits to improve the clarity of the summary's conclusion.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 7 (decision problem): We think there is a slight misrepresentation of the	"Volatile anaesthetics (which can be delivered via AnaConDa) are currently indicated for induction and maintenance of anaesthesia.	Sedana Medical has submitted SED001 RCT to the MHRA (and EMA) for use in sedation of adults. A paediatric study is ongoing and	The following sentence was added on page 9:

regulatory position for sedation of adults and paediatrics. This text is a little inaccurate: "The company stated that current regulation does not cover paediatric sedation with volatile agents in the intensive care setting, yet clinical experts noted that the regulation does not cover the use of volatile sedatives for adult patients in this setting either (see correspondence log)."	Volatile anaesthetics are not currently indicated for sedation of mechanically ventilated ICU patients, although they are used off-label in many settings. Sedana Medical has submitted a phase 3 RCT (SED001) to MHRA (and EMA) for approval of isoflurane via AnaConDa in adult patients."	may be submitted to the regulatory authorities in due course In addition, the clinical SLRs did not identify evidence relating to paediatric populations.	These volatile agents are though indicated for the induction and maintenance of anaesthesia and are already used off-label in the intensive care setting (see correspondence log). Sedana Medical has made submissions to the MHRA and the European Medicines Agency for approval of isoflurane sedation via AnaConDa for adult patients.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 11 Additional clarity needed	It could be clearer that FlurAbsorb is a longer term, larger capacity of the FlurAbsorb-S. Currently it sounds like you could use both simultaneously. Alternative placement as tidal volumes are lower, infusion rates are actually very similar or lower. This is mentioned but it could perhaps be clearer. We object to "leaked" – it's the small percentage of gas that passes through the AnaConDa membrane. It never leaks, it is still captured via the FlurAbsorb.	Additional clarity on technology	All below points relate to page 13 of the report: The report has a paragraph describing the different capacities ad timespans for which FlurAbsorn and FlurAbsorb-S can be used, therefore the EAC believes there is enough detail covering these technologies. The EAC added '; only one scavenging product can be used at a time' and amended the last sentence in that paragraph form 'These scavenging systems might require' to 'The scavenging system used might require' to emphasise the singular nature of the scavenging system used.

			The EAC has added '; this means that in practice similar sedative infusion rates are likely to be used when the device is placed in both positions' to clarify the issue as requested by the company. The word 'leaked' has been changed to 'expelled', a typo has been fixed and a note on the impact of the scavenging system has been added. The sentence now reads 'As such, the amount of the sedative agent expelled from the ventilator would not be notably larger than when used in the standard position, and the use of a scavenging system will protect staff from exposure to the sedative agent.'

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 "….failed to include the term anaconda"	"the company conducted a wider SLR of RCT (only) evidence directly comparing inhaled and IV sedation, in discussions (see correspondence log) they agreed that only studies including Anaconda should be included in this NICE appraisal."	The company search included all the RCTs that included AnaConDa.	This statement by the EAC occurs in two places: page 19 (section 4.1) and page 107 (section 9.1). The EAC, in both places, has highlighted that the company's searches were comprehensive. Nevertheless, the EAC is making here a specific comment that

			the particular search term 'anaconda' was not included in the company's search strategy; the EAC at this point is not commenting on the successfulness of the company's search strategy. The EAC's original statemen is factually accurate and as such does not require any change.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17: "….and the searches were eight months old,"	"the company submitted an updated search to their original SLR that was conducted on 14th April 2021"	Updated search was performed and submitted.	The EAC removed 'and the searches were eight months old,' from page 19 of the report. The EAC added a statement in Appendix A (subsection Company search strategy, screening criteria and process for economic evidence): The company also submitted an updated literature search that was conducted on the 14th of April 2021. The EAC believes that this change to page 19 better reflects the content of the paragraph. While the addition of the sentence in Appendix A is a better place to show the company's search strategy.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 70 (key outcomes) – typo 'sowed' not 'showed'.	'showed' not 'sowed'.	typo	The EAC changed 'sowed' to 'showed' on page 72 of the EAC report.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 73 (table 7, bottom) For SED001 95% CIs stated as 'not reported'	'reported in CSR as [redacted]	Submitted in SED001 CSR	The HR was added into the text. The EAC did not include measures of spread for other values where point estimates were given, so we did not include the 95%CI values here for consistency.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 73 (table 7, bottom) "no non-switchers results are reported"	This was the randomised study period (48+/-6h) so nobody had switched sedation regimen. (same applies for Table 8, page 76. There are no switchers at this time point).	correction	For page 73: The EAC has changed the statement to 'Analysis conducted on [redacted] patients (this was within the randomisation period, as such no patient switched sedation strategies).' To reflect the company's note but also to highlight the patient sample size.

			For page 79: The statement was changed to: All these assessments took place within the randomisation period, as such no patient switched sedation strategies. Also, two full stops were added at ends of sentences and an instance of double-spacing was deleted.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 77: "while the SED001 trial found patients in the isoflurane group had shorter ICU stays (though no assessment of statistical significance was made) compared to propofol patients (excluding patients that were switched between sedation methods within the 30-day follow-up)."	The company provided 'assessment of statistical significance', full CSR has [redacted] analysis, supplementary analysis of 'non-switchers' [redacted] also has stats analysis.	Assessment of statistical significance was made.	The EAC notes that the company provided analysis of ICU free days, but did not conduct an analysis of ICU length of stay. A sentence has been added on page 79 to make this point explicit [redacted] [redacted] Similarly '(though no assessment of statistical significance was made)' was removed.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 86: "no p-value given for full study population" (ICU Los)	It is in the CSR we provided [redacted]	Provided in CSR submitted to EAC	The EAC amended the sentence on page 89 to: [redacted] The EAC also changed a sentence on page 88 from [redacted] [redacted] so as to better reflect the CSR. The p-value is now also given on page 82 (bottom of table 9).

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 100: missing clinical study design issues in ICU setting	Interpretation of the clinical evidence: We suggest that this section needs to comment that study design issues in ICU RCTs (in general) mean that the longer-term outcomes	Clinical study design issues are relevant to the interpretation of SED001 ICU LoS data.	The EAC accepts the company's comment. We have added the following sentence 'This is particularly relevant for long-term outcomes, for which proving that benefit of anyone particular

	such as ICU stay have been harder to provide evidence on, SED001 is the largest RCT to do this.		intervention will be inherently difficult due to the type of care patients receive on ICU'. The EAC has already discussed the details of the SED001 trial elsewhere in the report, and as this section provides an interpretation of all the evidence, the EAC does not deem it necessary to single out the SED001 trial.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 105: As issue 3 above	As Issue 3 above		The EAC believes that this is relates to issue 4 above rather than 3. The EAC's response has been noted in issue 4.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 112-113: "The company submission does not provide details of how this was calculated but it appears to be the mean of the number of ventilator days for isoflurane and propofol reported in SED001."	The ventilation days set to mean for whole cohort (both arms) based on ns difference = 10.9 days	correction	Thank you for your comment. The EAC has added this information to the table on page 115 and 116 of the report.

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Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 115 – adding £621 per patient for training costs does seem extremely high. Appendix D shows method as: 6 hours training for 2 consultants at £119 per hour = £1428, 15 nurses at £60 per hour = £4788). "Total training cost for an ICU team to deliver inhaled sedation using AnaConDa device = £6216". Then assume this applies to 100 patients, so £6216/100 = £621 per anaconda patient.	We do think this is likely to be a considerable overestimate in reality for 2 key reasons: 1) £6216 training cost for an ICU team is likely much too high since in practice a large proportion of the Nurse training is or can be done concurrently with patient care. When we are doing bedside training and supporting their first set-up, syringe change and AnaConDa change, these literally take seconds from their bedside care routine. Consultant Anaesthetists are of course completely familiar with the use of volatiles in theatres. E-Learning takes 1 hour. Additional training is available but is not a necessity - do they have dedicated sessions on propofol and other IV's? 2) The training costs are likely to be mostly one-off and so the time horizon is longer and so the number of patients assumed in the denominator may be very much larger over time and much greater than the arbitrary assumption of 100.	Training costs in EAC report are likely over-estimated.	Thank you for your comment. The EAC agrees that the training costs included in the model are likely an over-estimate of the true cost of training. The EAC consider that this has been noted clearly in the report and it has been acknowledged that the inclusion of such high costs is a conservative estimate and likely to be much lower however this should be discussed by the experts and committee. The EAC has not made any changes.

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Sedana Medical
Submission date	27th April 2021
Regulatory documents attached	Please list regulatory documents submitted: - CE certificate - Instructions for use  CE-667826.pdf  IFU_Adults_1020-final.pdf
Contains confidential information	Yes

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1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People who are invasively ventilated in intensive care using a mechanical ventilator but not a high frequency ventilator.	Agreed	n/a
Intervention	AnaConDa-S AnaConDa (previous version)	These are not two different interventions. The AnaConDa-S (50ml) device is a product development of AnaConDa (100ml) with a reduced dead space.	NICE MIB229 cited 2 studies (Marcos-Vidal et al. 2020; Bomberg et al. 2018) that show the 2 versions are comparable in sedation efficiency and that the 'S' version has the benefit of lower carbon dioxide rebreathing. In SED001 RCT, 86 (57.3%) of all isoflurane patients used the larger (100 mL) device and 64 (42.7%) used the small (50 mL) device.
Comparator(s)	IV sedatives Standard vaporiser	Direct evidence is available for inhaled sedation via AnaConDa compared to IV sedatives. The AnaConDa device is not compared with other means of delivering inhaled sedation.	
Outcomes	a. wake-up time after ICU sedation b. cognitive recovery c. sedation efficacy (time to extubating, proportion of time within desired sedation level and titration ability using the Richmond Agitation-Sedation Scale) d. markers of cardiac injury, liver, gut, kidneys and brain for short-term operative sedation e. sedation effectiveness in patients with life-threatening	The clinical evidence in this submission is based primarily on the SED001 RCT supported by a SLR (22 published RCTs). Much evidence is available on the following endpoints: sedation efficacy (c) (including amount of opioid drug used (p)); wake-up times (a); cognitive recovery (b); duration of mechanical ventilation (j); length of stay in the ICU (k); and adverse-events (q). Evidence on outcomes d, e, f, g, h, i, l is more limited. Staff time in the ICU (o) is not included here but is incorporated into the economic evidence submission. The amount of volatile anaesthetic agent used (m) and staff exposure to volatile anaesthetic agents (n) are included in the environmental impact and sustainability considerations (below).	

	bronchospasm and asthma f. oxygenation and inflammatory markers in patients with ARDS g. psychological outcomes (e.g. memories of hallucination, and long-term psychological morbidity, PTSD) h. Effectiveness of ventilation on people with bronchoconstriction i. Reduction of additional bronchodilators j. duration of mechanical ventilation/ increased ventilator-free days k. length of stay in the ICU l. hospital length of stay/ hospital-free days. m. Amount of volatile anaesthetic agent used n. Staff exposure to volatile anaesthetic agents o. Staff time in the ICU p. Amount of opioid drug used q. Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, including threshold analysis. Different cost scenarios of uptake of the AnaConDa device are included. Analysis of different combinations of devices will not be included.	Inhaled sedation via AnaConDa device will be compared with standard-of-care IV sedation only.

	address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	People with acute asthma that need to be mechanically ventilated. People with acute respiratory distress syndrome that need to be mechanically ventilated Children that need to be mechanically ventilated Patients who need to have regular neurological wake up tests performed People who are intolerant to IV sedation (e.g people who misuse alcohol, people who misuse drugs, people on overdose, people with COVID-19) People with hepatic and renal failure People with super-refractory status epilepticus People under prolonged sedation who need an IV sedation break (due to being at risk of developing tolerance, tachyphylaxis and/or propofol infusion syndrome)	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	AnaConDa-S
Approved name	AnaConDa-S
CE mark class and date of authorisation	CE-certified (by BSI) according to European Medical Device Directive 93/42/EEC (as a risk classification IIa according to Annex IX) and has been on the EU market since 2005
Instructions for use:	AnaConDa User Guide: About AnaConDa (Using AnaConDa, User Guide) - Sedana Medical

Version(s)	Launched	Features
AnaConDa	2005	100ml dead space
AnaConDa-S	2017	50ml dead space - lower carbon dioxide rebreathing

Figure 1: Image of AnaConDa-S device

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
AnaConDa-S is associated with: • Reliable, sustainable sedation efficacy (maintaining adequate sedation, lower opioid use, more spontaneous breathing, improved oxygenation, and reduced time to extubation) • Shorter, more predictable wake up time after ICU sedation • Improved cognitive recovery/ psychological outcomes • Shortened duration of mechanical ventilation and time in ICU	SED001 RCT, SLR	More flexible clinical management and control of sedation (avoiding accumulation), patients experience faster wake-up and cognitive recovery which enables reduced time to extubation, less time on a ventilator and faster discharge from ICU.
System benefits		
AnaConDa-S is associated with: • A reduction in length of stay in the ICU, including less time supported by mechanical ventilation • A reduction in hospital length of stay/ increased hospital- free days	SED001 RCT, SLR	
Cost benefits		
AnaConDa-S has potential to be cost-saving compared with (SoC) IV sedation	Cost-consequence model	Reduced ICU length-of-stay (including time supported by mechanical ventilation) as well as less frequent sedation administration (dose renewals) and less need for daily sedation interruption (DSI) protocols provides cost-savings.
Sustainability benefits		
Reduction in volatile anaesthetic use via the anaesthetic conserving function of AnaConDa-S.	TBA	The volatile anaesthetic exhaled by the patient is retained by the AnaConDa-S reflector, and 90 % is resupplied during

		the next inspiration, thereby reducing waste of the sedative gas.

In addition, there is some evidence of benefits from AnaConDa for specific patient groups:

- Potential reduction in markers of cardiac, liver, gut, kidneys, and brain injury
- Effective sedation in patients with life-threatening bronchospasm and asthma

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The Anaesthetic Conserving Device-S (AnaConDa-S; Sedana Medical) is a volatile anaesthetic delivery system to give isoflurane or sevoflurane to people who are invasively ventilated, usually in an intensive care setting.

AnaConDa-S is a single-use device (replaced every 24 hours or when needed). The device can be inserted into either the breathing circuit of a ventilator between the endotracheal tube and Y piece, replacing the heat and moisture exchanger (standard placement) or in the inspiratory port of the ventilator (alternative placement). Liquid anaesthetic is injected through the anaesthetic agent line, into a porous rod in the AnaConDa-S device where the anaesthetic is vaporised. The vaporised anaesthetic is then inhaled by the patient with the inspiration flow from the ventilator. With continued breathing, the majority of anaesthetic agent that has not been absorbed by the lungs is exhaled and adsorbed by an active carbon filter in the device. On further inhalation, the anaesthetic is desorbed from the filter and transported back to the lungs, reducing the amount of anaesthetic agent wasted. The AnaConDa- S device also contains a bacterial and viral filter and a gas analyser port. This port is used to measure the exhalated anaesthetic concentration in minimal alveolar concentration (MAC value; a relative measure of the level of anaesthesia) or end-tidal concentration (Fet%). Side stream or mainstream gas monitors, which can measure concentrations of carbon dioxide and anaesthetic gases, must be used to continually monitor anaesthesia, these will need to be purchased separately if not already available.

AnaConDa-S can be used with almost any kind of ventilator, except high-frequency ventilators. It was launched in the UK in 2017 and is a newer version of the AnaConDa device (available in the UK since 2005), which is now only available on request in the UK. The AnaConDa-S has a lower dead space of 50 ml (compared with 100 ml in the original device) and works with tidal volumes as low as 90ml. The lower dead space allows AnaConDa-S to be used on smaller adults or children who have smaller minute or tidal ventilation.

The intended place in therapy for AnaConDa-S would be as an alternative to IV sedation, that provides more flexible clinical management as patients experience faster wake-up and cognitive recovery, which enables reduced time to extubation, less time on a ventilator and faster discharge from ICU/hospital.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Isoflurane is a greenhouse gas, its ozone depletion impact is, however, considered low due to a) the short atmospheric lifetime of isoflurane and b) diligent control of risk of leakage.

The AnaConDa set-up with adapted couplings and connectors is customized for sedation in ICU to simplify use and minimize risk of leakage. The gas pollution in ICU with AnaConDa set-up is minimal, room pollution levels are below 1.5 PPM and significantly below external thresholds for safety (Herzog-Niescery et al. 2018; Sackey et al. 2005). An effective carbon filter in the AnaConDa allows more than 90% of the exhaled anaesthetic to be adsorbed during expiration and reflected to the patient during inspiration, reducing the drug consumption.

Active or passive scavenging is recommended to eliminate the exhaust gases from the ventilator and gas monitor and has shown to decrease the level of waste gas to recommended levels. Sedana Medical provides the FlurAbsorb, a passive gas scavenging filter. The large one was released in 2013 and in 2018, a smaller device was released, the FlurAbsorb-S which can be replaced every 24 hours, along with the AnaConDa. The FlurAbsorb is a plastic container which contains highly absorbent activated charcoal pellets for the removal of waste anaesthetic gases. The FlurAbsorb has a capacity of up to 10 syringes of 50 ml (total 500 ml) and the smaller FlurAbsorb-S has a capacity of up to 3 syringes of 50 ml (total 150 ml).

Once the syringe pump has stopped, there is only a small amount of anaesthetic gas in AnaConDa. Most of the isoflurane is bound to the filter when there is no flow through the AnaConDa and therefore no gas is released. The AnaConDa and empty syringes are disposed of according to local hospital protocols. It is recommended that FlurAbsorb and syringes with larger amounts of residual anaesthetic gas (>20 ml) be disposed of with the special hospital waste. UK Department of Health provide guidance setting out best practice guidelines for waste segregation and disposal through a colour coding system: Types of healthcare waste (publishing.service.gov.uk)

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

Sedatives are frequently administered to critically ill patients to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm (Barr et al., 2013). Sedation of ICU patients is vital for critical care and is required by >85% of patients to reduce ICU and hospital stay, increase survival, and facilitate mechanical ventilation (Weinert et al., 2007; Jerath et al., 2017). Sedatives and analgesics support tolerance of mechanical ventilation in postoperative patients.

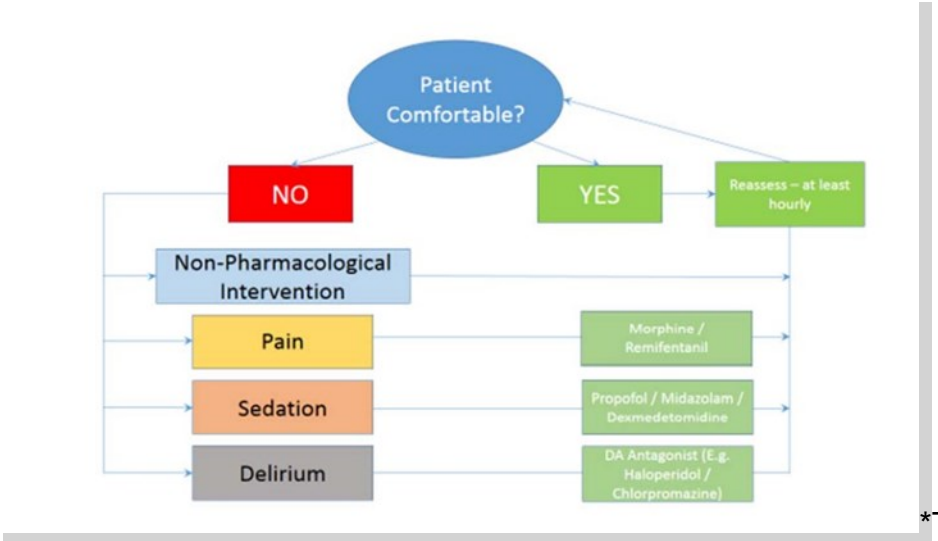
Today, sedation in mechanically ventilated ICU patients is generally achieved by the intravenous infusion of propofol, midazolam or alpha-2-adrenergic agonists such as dexmedetomidine, in combination with opioids. However, each of these agents has limitations. Midazolam is associated with development of major side-effects such as the development of delirium, development of tolerance in some patients and long, unpredictable wake-up times, particularly in the face of organ dysfunction. High doses or prolonged use of propofol increase the risk of PRIS, a potentially lethal side-effect. Dexmedetomidine is mildly sedative and is not a viable treatment option for a substantial proportion of mechanically ventilated patients in need of sedation in the range of RASS -1 to -4 and moreover is associated with risks of bradycardia and asystole.

The PADIS 2018 guideline (Devlin et al., 2018) suggests using propofol over a benzodiazepine for sedation in mechanically ventilated adults after cardiac surgery (conditional recommendation, low quality of evidence) and they suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence). These medications may predispose patients to increased morbidity (Kollef et al., 1998; Pandharipande et al., 2006). In critically ill patients, unpredictable pharmacokinetics and pharmacodynamics secondary to drug interactions, organ dysfunction, inconsistent absorption and protein binding, hemodynamic instability, and drug accumulation can lead to adverse events and a

high risk for the development of delirium (Barr et al., 2013; Roberts et al., 2012; MacKenzie et al., 2017; Devlin et al., 2018).

The UK Intensive Care Society guidelines

Intensive Care Society Review of Best Practice for Analgesia and Sedation in the Critical Care, 2014, (https://www.ics.ac.uk/ICS/GuidelinesAndStandards/ICSGuidelines.aspx) details a clinical care pathway for analgo-sedation in ICU (figure below). These ICS Guidelines report the most commonly used agents are intravenous anaesthetic agents or benzodiazepines, often in combination with opioids. Other options to control agitation, delirium and pain in the ICU include alpha 2 agonists such as clonidine and dexmedetomidine, ketamine, non-opioid analgesics and antipsychotic agents. There is insufficient evidence to recommend one regimen over another, and so the agents chosen should be individualized to the patient's requirements, characteristics and the clinical situation. However, the current literature supports modest benefits in outcomes with non-benzodiazepine-based sedation versus benzodiazepines (Barr et al., 2013).



*The well-known pharmacological properties of isoflurane as a sedation medicine: rapid on/ offset and minimal metabolism and thus organ toxicity offer greater potential for clinical management flexibility and controllability of mechanically ventilated patients.

Isoflurane has been used off-label for sedation since the 1980´s and there are a number of randomised controlled studies, comparing efficacy and safety of isoflurane with midazolam or propofol. The pharmacological properties and clinical evidence for isoflurane sedation demonstrate the absence of clinically significant accumulation or active metabolites, making

isoflurane a useful alternative for patients tolerant to IV sedatives, and also for patients with compromised hepatic or renal function. These organ systems are often affected in the critically ill ICU patient. Emergence, in terms of time from drug stop until extubation and cognitive recovery is rapid, typically within 10 to 60 minutes (Hanafy, 2005; Kong et al., 1989; Sackey et al., 2004; Spencer and Willatts, 1992). Its use in routine clinical practice was, however, severely limited by a reliance on bulky, impractical, and expensive anaesthesia machines normally used in surgical theatres and not suitable for ICU environments. The introduction of the anaesthetic conserving device (AnaConDa) paired with concerns regarding intravenous sedatives has led to broad unlicensed use of inhaled anaesthetics for sedation in the ICU, mainly in Europe, with more than 500,000 units sold to date.

More recently some clinical guidelines have recognised the role of volatile inhaled anaesthetics for the sedation of mechanically ventilated patients in ICU.

Evidence and consensus-based German guidelines (DAS Taskforce, 2015) for the management of analgesia, sedation, and delirium in intensive care unit recommends that aside from propofol, volatiles are also a feasible option.

The American Society of Anaesthesiologists (ASA/APSF, 2020) have recommended use of volatile anaesthetic for sedation of ICU patients in response to the COVID-19 pandemic (ASA/APSF (2020) Guidance for Use of Volatile Anesthesic for Sedation of ICU Patients Emergency Use for the COVID-19 Pandemic) stating:

“Long term volatile sedation would be an off-label use of these drugs in the US. In Europe and Canada, critical care providers have been practicing long term volatile anaesthetic sedation with either Isoflurane or Sevoflurane for nearly a decade. Experience in these locations suggests that these agents are effective sedatives with rapid on/offset and minimal metabolism and thus organ toxicity, even after multiple days of administration. Patients typically wake up quickly and have short times to extubation after sedative discontinuation as compared to other regimens including Propofol.”

NICE in the UK have published advice as a ‘Medtech Innovation Briefing’ to support the AnaConDa-S for sedation with volatile anaesthetics in intensive care (NICE MIB229, 2020).

*Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Sedana Medical is committed to providing support and training for adoption of the AnaConDa-S device in ICUs. In order to meet the individual educational needs and goals of each Critical Care Unit, Sedana Medical meet with key staff and identify their needs, develop a joint educational plan, and implement using the most appropriate strategies to attain, efficiently and effectively, those needs and professional competencies. Sedana Medical routinely train all professions allied to health, including EBME, Physiotherapy, Pharmacy, Medical and Nursing staff. Learning resources include:

- fully CPD Accredited e Learning
- bedside education and set-up support
- classroom educational sessions
- train the trainer education
- user guides / reference materials
- peer to peer online meetings enabling NHS-wide development and support
- national and international conference attendance – sponsored symposia
- quality and regulatory sign-off before new Hospitals are Approved as Customers

All Sedana Medical staff are MIA Tier 3 registered to facilitate training in high-risk patient areas. All UK Staff have been Covid vaccinated and fit tested for FFP3.

Further training is provided via webinars, quick-guides, handouts, memory cards and YouTube videos to reinforce learning and update practitioners on new developments. Sedana Medical training resources available online include:

About Us (E-learning-Start) - Sedana Medical

About AnaConDa (Using AnaConDa, User Guide) - Sedana Medical

4 *Published and unpublished clinical evidence

Identification and selection of studies

Clinical evidence in support of AnaConDa is based on three key sources:

1. **Phase 3 SED001 (N=301) RCT (recently completed) comparing isoflurane/anaconda vs. propofol (unpublished, Sedana data on file):**

The primary objective was meet: Sedation with isoflurane, using the AnaConDa delivery system, was non-inferior to propofol in terms of maintaining adequate sedation without rescue sedation, with success rates above 90% for both groups. Patients receiving isoflurane had a shorter and more predictable time to wake-up after 48 hours of sedation (p=0.001). A post-hoc analysis (excluding patients who switched sedation regimen within 30day follow-up) found that the isoflurane group had significantly shorter duration in ICU (12.7 days vs. 16.9 days, p=0.008).

2. **A Systematic Literature Review (SLR) of 22 published clinical RCT studies directly comparing inhaled with intravenous sedation:**

The inhalational agents were found to be associated with significantly faster extubation, sedation stabilisation, and emergence than intravenous agents. All other outcomes i.e., hospital stay, time spent in the target range, delusions, safety either indicated an advantage for inhalational agents or were comparable between inhalational and intravenous agents.

3. **A review of observational clinical studies directly comparing inhaled with intravenous sedation:**

Three non-randomised (excluded from SLR above), observational studies (Staudacher et al., 2018; Bellgardt et al., 2016; Krannich et al., 2017) were noted to be of significant interest to support the clinical and health economic evidence. These studies showed that isoflurane sedation is feasible during targeted temperature management. Time to spontaneous breathing and ICU stay was shorter for isoflurane patients, but this did not show statistical significance (Staudacher et al. 2018). After sedation with isoflurane, the in-hospital mortality and 365-day mortality was significantly lower than after propofol/midazolam sedation: 40 versus 63% (P =

0.005) and 50 versus 70% (P= 0.013), respectively (Bellgardt et al., 2016). A matched pairs analysis revealed that time on ventilator (difference of median, 98.5 hr; p = 0.003) and length of ICU stay (difference of median, 4.5 d; p = 0.006) were significantly shorter in patients sedated with isoflurane when compared with IV sedation (Krannich et al. 2017).

Summary information about the number of studies identified in the SLR is provide in Table 1. A detailed description of the search strategy used, and a detailed list of any excluded studies, is provided in appendix A.

Table 1: Studies identified in the SLR

Number of studies identified in a systematic search.		3546
Number of studies identified as being relevant to the decision problem.		22 (in 31 pubs)
Of the relevant studies identified:	Number of published studies (included in table 1).	20
	Number of abstracts (included in table 2).	2
	Number of ongoing studies (included in table 3).	

A summary of the main comparisons included in the SLR can be found below in Figure 2 .

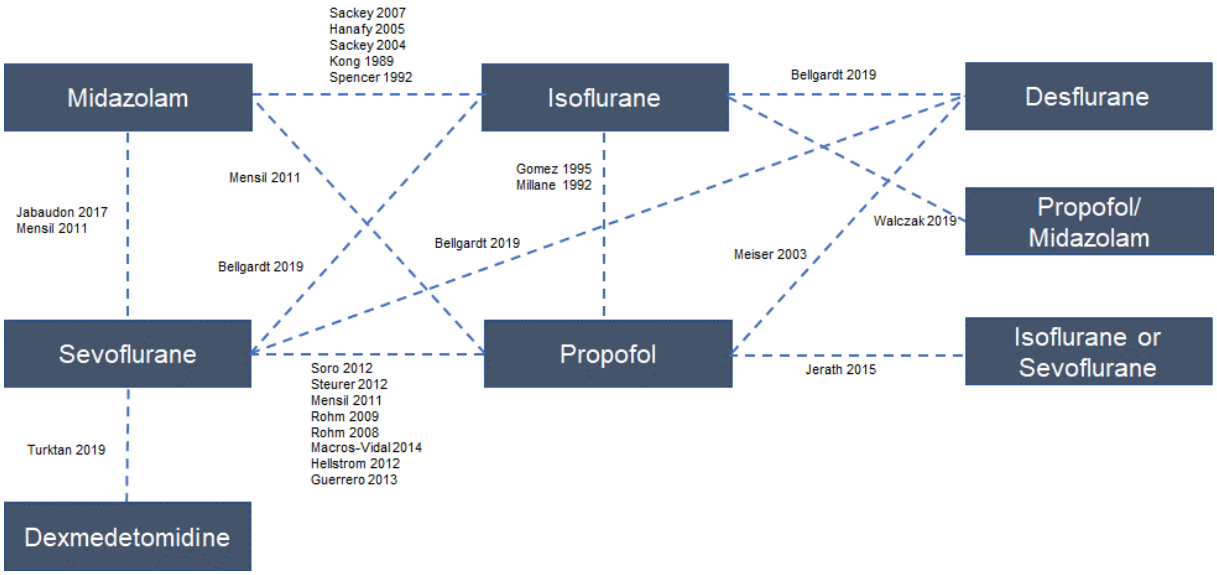


Figure 2: Summary of main comparisons included in the SLR

Note: All studies included AnaConDa except those that pre-dated launch of the AnaConDa device (Kong 1989, Spencer 1992, Millane 1993, Gomez 1995, Meier 2003) and Bellgardt 2019 (MIRUS device)

List of relevant studies

The SLR was conducted with the broad objective to provide a narrative summary of the efficacy, safety, and tolerability evidence for inhalational versus intravenous sedatives among mechanically ventilated adult patients in ICU. The search was not restricted by sedative drug or by type of device used to support inhalational sedatives. The SLR followed the standard methodology for conducting systematic reviews as per guidelines provided by the NICE and the Cochrane handbook. The results of this review are reported as per the PRISMA guidelines.

Brief details of all studies identified as being relevant to the decision problem are provided below. Table 2 summarises details of 20 published RCTs identified in the SLR. Table 3 summaries 2 conference abstracts identified in the SLR.

A summary of the recently completed SED001 Phase 3 RCT (Sedana Medical) is provided in

Table 4. This is the biggest (N=301) randomised clinical trial of this duration to date comparing inhaled isoflurane sedation using AnaConDa with IV propofol in mechanically ventilated ICU patients and is currently under discussion with European regulatory authorities. The SED001 RCT will be fully published in due course but for this NICE clinical submission is unpublished confidential (detailed in appendix C) evidence. As an unpublished study, a structured abstract is provided in appendix A. As this is company information, Sedana Medical holds full details of SED001 RCT CSR on file.

Table 5 provides a summary of 3 observational studies identified as relevant to the decision problem.

For the SLR a systematic database search was performed on 3rd August 2020 identified, these results are included. However, an additional update of these searches was performed for this NICE submission on 14th April 2021. The SLR update (searches refresh from July 2020 to 14th April 2021) identified 3 further publications considered of potential relevance, details of the SLR update are added into appendix A.

Results of all studies are provided in Table 6 below.

Table 2: Summary of all relevant published RCT studies

Study name (Trial name)	Publication type	Blinding	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
Sackey 2007	Journal Article	Single-blind	Sweden	Single centre	ICU patients	>12 hours	Isoflurane	Midazolam	AnaConDa	R: 20 C: 20	Sackey 2007
Hanafy 2005	Journal Article	Open label	Egypt	Single centre	Cardiac surgery	≤24 hours	Isoflurane	Midazolam	AnaConDa	R: 24 C: 24	Hanafy 2005
Sackey 2004	Journal Article	Single-blind	Sweden	Single centre	ICU patients	>12 hours	Isoflurane	Midazolam	AnaConDa	R: 40 C: 40	Sackey 2004
Spencer 1992	Journal Article	NR	United Kingdom	Single centre	ICU patients	>24 hours	Isoflurane	Midazolam	Siemens isoflurane vaporiser 952	R: 100 C: 46	Spencer 1992
Kong 1989	Journal Article	Double-blind	United Kingdom	Single centre	ICU patients	≤24 hours	Isoflurane	Midazolam	Siemens isoflurane vaporiser 952	R: 60 C: 58	Kong 1989
Jerath 2015	Journal Article	Open label	Canada	Single centre	Cardiac surgery	<24 hours (Author: short term)	Isoflurane or Sevoflurane	Propofol	AnaConDa	R: 157 C: 141	Jerath 2015
Gomez 1995	Journal Article	NR	Spain	Single centre	Cardiac surgery	NR (Author: short term)	Isoflurane	Propofol	Ohmeda Portable Drawover Vaporizer	R: 40 C: 40	Gomez 1995
Millane 1992	Journal Article	NR	United Kingdom	Single centre	ICU patients	48 hours	Isoflurane	Propofol	Mark 3 Isotec vaporizer	R: 13 C: 7	Millane 1992
Jabaudon 2017 (SEGA)	Journal Article	Open label	France	Single centre	ARDS	48 hours	Sevoflurane	Midazolam	AnaConDa	R: 50 C: 50	Jabaudon 2017
Marcos-Vidal 2014	Journal Article	Open label	Spain	Single centre	Cardiac surgery	>2 hours	Sevoflurane	Propofol	AnaConDa	R: 144 C: 129	Marcos-Vidal 2014
Guerrero 2013	Journal Article	Single-blind	Spain	Single centre	Cardiac surgery	NR	Sevoflurane	Propofol	AnaConDa	R: 60 C: 60	Guerrero 2013
Soro 2012	Journal Article	Double-blind	Spain	Single centre	Cardiac surgery	≥4 hours	Sevoflurane	Propofol	AnaConDa	R: 75 C: 73	Soro 2012

Study name (Trial name)	Publication type	Blinding	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
Steurer 2012	Journal Article	Open label	Switzerland	Single centre	Cardiac surgery	≥4 hours	Sevoflurane	Propofol	AnaConDa	R: 117 C: 102	Steurer 2012
Hellstrom 2012	Journal Article	Single-blind	Sweden	Single centre	Cardiac surgery	>2 hours	Sevoflurane	Propofol	AnaConDa	R: 100 C: 89	Hellstrom 2012
Mesnil 2011	Journal Article	Open label	France	Single centre	ICU patients	> 24 hours up to 96 hours	Sevoflurane	Propofol; Midazolam	AnaConDa	R: 60 C: 47	Mesnil 2011
Rohm 2009	Journal Article	Single-blind	Germany	Single centre	Major surgeries	≤24 hours	Sevoflurane	Propofol	AnaConDa	R: 130 C: 125	Rohm 2009
Rohm 2008	Journal article	Single-blind	Germany	Single centre	Cardiac surgery	<24 hours (Author: short term)	Sevoflurane	Propofol	AnaConDa	R: 70 C: 70	Rohm 2008
Turktan 2019	Journal Article	NR	Turkey	Single centre	ICU patients with pulmonary disorders	<48 hours	Sevoflurane	Dexmedetomidine	AnaConDa	R: 30 C: 30	Turktan 2019
Meiser 2003	Journal Article	Open label	Germany	Single centre	ICU patients	Avg. 10.6 hours	Desflurane	Propofol	Modified TEC-6 vaporizer	R: 60 C: 56	Meiser 2003
Bellgardt 2019	Journal Article	Single-blind	Germany	Single centre	Surgery (Various)	>2 hours up to 96 hours	Isoflurane	Sevoflurane; Desflurane	MIRUS	R: 30 C: 30	Bellgardt 2019

AnaConDa: Anaesthetic Conserving Device; ARDS: Acute Respiratory Distress Syndrome; C: Number of trial completers; ICU: Intensive care unit: NR: Not reported; R: Number of randomised patients

Table 2a: Summary of additional relevant published RCT studies (SLR Update 14th April 2021)

Study name (Trial name)	Publication type	Blinding	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
Guinot 2020	Journal Article	Open label	France	Single centre	ICU patients	NR	Sevoflurane	Propofol	MIRUS	R: 42 C: 39	Guinot 2020
Daume 2021	Journal Article	Open label	Germany	Single centre	ICU patients	≤24 hours	Isoflurane	Desflurane	MIRUS	R: 10 C: 10	Daume 2021

Table 3: Summary of abstracts

Study name (Trial name)	Publication type	Blinding	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	NCT ID
El 2016	Conference abstract	NR	Egypt	Single centre	Cardiac surgery	NR	Inhalational (not specified)	Intravenous (not specified)	NR	R: 60 C: NR	NR
Walczak 2019; VALTS sub study	Conference abstract	Open label	Canada	Multiple Centres	ICU patients	>48 hours	Isoflurane	Propofol/ midazolam	AnaConDa	R: 60 C: 24 (sub-study)	NCT 01983800

Table 3a: Summary of additional abstracts (SLR Update 14th April 2021)

Study name (Trial name)	Publication type	Blinding	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
Meiser 2020 (First report of SED001)	Conference abstract	Open label	Germany Slovenia	Multiple centre	ICU patients	48h+/-6h	Isoflurane	Propofol	AnaConDa	301	EudraCT 2016-004551-67

Table 4: Summary of all relevant unpublished studies

Study name (Trial name)	Publication type	Blinding	Study phase	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
SED001	Unpublished	Open label	Phase 3	Germany, Slovenia	Multiple centres	ICU patients	48h+/-6h	Isoflurane	Propofol	AnaConDa	301	EudraCT 2016-004551-67

Table 5: Summary of relevant observational studies

Study name (Trial name)	Publication type	Study Design	Country	Setting	Indication	Sedation duration	Intervention	Comparator	Mechanical ventilation device	Sample size	Link
Staudacher et al., 2018	Journal Article	Single centre registry case analysis using propensity score matching	Germany	Single centre	ICU patients	>48h	Isoflurane	Propofol	AnaConDa	214	Staudacher 2018
Bellgardt et al., 2016	Journal Article	Single centre retrospective cohort study	Germany	Single centre	ICU patients	>96h	Isoflurane	Propofol Midazolam	AnaConDa	369	Bellgardt 2016
Krannich et al., 2017	Journal Article	Single centre retrospective cohort study	Germany	Single centre	ICU patients	>48h	Isoflurane	Standard IV sedation	AnaConDa	432	Krannich 2017

Table 6 : Results of all relevant studies

Study	Results	Company comments
Pivotal registration study (unpublished):		
SED001 (CSRSED001, Sedana Medical - data on file) **NOTE: SLR update (14th April 2021) identified first conference abstract publication from SED001 (Meiser et al., 2020)**	[redacted]	The clinical trial (SED001) was not designed to demonstrate superiority on long-term outcomes, it was designed to provide proof of non-inferiority to sedation standard of care (Propofol) in order to meet regulatory label objectives. The duration of the randomised study was 48±6h hours after which the subject's study treatment was ended, after all the study related assessments had been completed the sedation or follow-up monitoring could continue according to local practice as deemed necessary by the treating physician. Hence after 48±6h hours some patients switched sedation regimen from that assigned by randomisation in the study.
RCT Studies identified by SLR:		
Sackey 2007	Bispectral index™ does not reliably predict sedation depth as measured by clinical evaluation in non-paralysed ICU patients sedated with isoflurane or midazolam (in an RCT).	AnaConDa device included.
Hanafy 2005	Wake-up times were significantly shorter in the isoflurane group where time to extubation [mean (SD)] was 15.2 (5.3) min and in the midazolam group 120.1 (30.3) min, P value = 0.01. Time to follow verbal command was 16.3 (3.2) min versus 60.4 (20.4) min for the isoflurane group and midazolam group, respectively, P value = 0.03. Patients in the isoflurane group were mobilized significantly earlier from bed 8 (1.8) h,	AnaConDa device included.

	compared to 14 (3.3) h in midazolam group, P value < 0.05. No serious complications related to either sedative drug occurred.	
Sackey 2004	Wake-up times were significantly shorter in the isoflurane group than in the control group (time to extubation [mean ± SD] 10 ± 5 vs. 252 ± 271 mins, time to follow verbal command 10 ± 88 vs. 110 ± 132 mins). Proportion of time within the desired sedation interval was comparable between groups (isoflurane 54%, midazolam 59% of sedation time).	AnaConDa device included.
Spencer 1992	There was no difference in any of the physiological or biochemical variables recorded between the two groups. Patients sedated with isoflurane recovered more rapidly and were weaned from mechanical ventilation sooner than those sedated with midazolam.	Study pre-dated AnaConDa device
Kong 1989	Isoflurane produced satisfactory sedation for a greater proportion of time (86%) than midazolam (64%), and patients sedated with isoflurane recovered more rapidly from sedation.	Study pre-dated AnaConDa device
Walczak 2019	24/36 patients (66.7%) survived to hospital discharge; 4 died in ICU; 24 completed 3-months follow-up. 21/36 patients received inhaled isoflurane volatile sedation. Incident delirium was 42.1% in the volatile sedation group as compared to 53.9% in the intravenous sedation group (p=0.51). A trend towards improved cognitive performance at 3 months follow-up was seen in the patients who received isoflurane as compared to intravenous sedation, 41.1% and 22.2 % were unimpaired, respectively (p=0.33).	Conference abstract. AnaConDa device included.
Jerath 2015	Patients sedated using inhaled volatile agent displayed faster readiness to extubation time at 135 minutes (95-200 min) compared with those receiving IV propofol at 215 minutes (150-280 min) (p < 0.001). Extubation times were faster within the volatile group at 182 minutes (140-255 min) in comparison with propofol group at 291 minutes (210-420 min) (p < 0.001). The volatile group showed a higher prevalence of vasodilatation with hypotension and higher cardiac outputs necessitating greater use of vasoconstrictors. There was no difference in postoperative pain scores, opioid consumption, sedation score, ICU or hospital length of stay, or patient mortality.	AnaConDa device included.
Gomez 1995	Statistically significant differences were found for stabilization of sedation time (4 min +/- 1.17 for isoflurane and 11.7 min +/- 4.78 for propofol) and time to endotracheal extubation (56.2 min +/- 20.47 for isoflurane and 72.65 min +/- 30.90 for propofol), number of times dosage had to be changed (2.20 +/- 0.89 with isoflurane and 7.05 +/- 2.58 with propofol) and time of administration had to be interrupted (8.45 min +/- 8.73 with propofol and 0.75 min +/- 1.94 with isoflurane).	Study pre-dated AnaConDa device
Millane 1992	Twenty-four patients predicted to require artificial ventilation for at least 48 h were entered into a randomised crossover study to monitor sedation quality and time to recovery from sedation. There were no significant differences between the two agents	AnaConDa device included.

	in either end-point, with over 95% optimal sedation achieved by the use of each drug. Few adverse events were noted. Technological advances in the administration of volatile agents as long-term sedatives in the Intensive Care Unit may facilitate their more widespread use.	
Jabaudon 2017	There was a significant reduction over time in cytokines and soluble form of the receptor for advanced glycation end-products levels in the sevoflurane group, compared with the midazolam group, and no serious adverse event was observed with sevoflurane. In patients with ARDS, use of inhaled sevoflurane improved oxygenation and decreased levels of a marker of epithelial injury and of some inflammatory markers, compared with midazolam.	AnaConDa device included.
Marcos-Vidal 2014	Data from 129 patients, 62 sedated with propofol and 67 with sevoflurane, were analyzed. The analysis of the troponin T levels showed differences 12 and 48 hours after admission. Mean values at 12hours were 0.89 (standard deviation 0.55) µg.L(-1) in the propofol group and 0.69 (standard deviation 0.40) µg. L(-1)in the sevoflurane group (p = 0.026). TnT levels at 48hours were 0.60 (standard deviation 0.46) µg.L-(1)in the propofol group and 0.37 (standard deviation 0.26) µg.L(-1)in the sevoflurane group (p = 0,007). No differences were found in the groups in the creatinine levels before discharge. The post-operative sedation with sevoflurane after cardiac surgery with cardiopulmonary bypass is a valid alternative to propofol. It does not increase the number of side effects related to kidney damage in patients with no prior renal disease, leading to reduced troponin T levels 12and 48hours after admission.	AnaConDa device included.
Guerrero 2013	There were significant differences between group SS and the other 2 groups in the levels of N-terminal pro-brain natriuretic peptide (SS [501±280 pg/mL] compared with SP [1270±498 pg/mL] and PP [1775±527 pg/mL] [P<.05]) and troponin I (SS [0.5±0.4 ng/mL] compared with SP [1.61±1.30 ng/mL] and PP [2.27±1.5 ng/mL] [P<.05]) and a lower number of inotropic drugs. Sevoflurane administration in patients undergoing off-pump coronary artery bypass graft, in the operating room and the intensive care unit, decreases myocardial injury markers compared with patients who only received sevoflurane in the intraoperative period, but both were a better option to decrease levels of myocardial markers when compared with the propofol group.	AnaConDa device included.
Soro 2012	Necrosis biomarkers increased significantly in the postoperative period in both groups with no significant differences at any time. Inotropic support was needed in 72.7 and 54.3% of patients in the propofol and sevoflurane groups, respectively (P = 0.086). There were no significant differences in haemodynamic variables, incidence of arrhythmias, myocardial ischaemia or and lengths of stay in the ICU and hospital between the two groups. In patients undergoing coronary bypass graft surgery, continuous administration of sevoflurane as a sedative in the ICU for at least 4 h	AnaConDa device included.

	postoperatively did not yield significant improvements in the extent and time course of myocardial damage biomarkers compared to propofol.	
Steurer 2012	Fifty-six patients were analyzed in the propofol arm, and 46 patients in the sevoflurane arm. Treatment groups were comparable with regard to patient demographics and intraoperative characteristics. Concentration of troponin T as the most sensitive marker for myocardial injury at POD1 was significantly lower in the sevoflurane group compared with the propofol group (unadjusted difference, -0.4; 95% CI, -0.7 to -0.1; P < 0.01; adjusted difference, -0.2; 95% CI, -0.4 to -0.02; P = 0.03, respectively). The data presented in this investigation indicate that late postconditioning with the volatile anesthetic sevoflurane might mediate cardiac protection, even with a late, brief, and low-dose application.	AnaConDa device included.
Hellstrom 2012	Median time from drug stop to extubation (interquartile range/total range) was shorter after sevoflurane compared to propofol sedation; 10 (10/100) minutes versus 25 (21/240) minutes (p <0.001). Time from extubation to adequate verbal response was shorter (p =0.036). No differences were found in secondary endpoints. Sevoflurane sedation after cardiac surgery leads to shorter wake-up times and quicker cooperation compared to propofol. No differences were seen in ICU-stay, adverse memories or recovery events in our short-term sedation.	AnaConDa device included.
Mesnil 2011	Forty-seven patients were analyzed. Wake-up time and extubation delay were significantly (P<0.01) shorter in group S (18.6 ± 11.8 and 33.6 ± 13.1 min) than in group P (91.3 ± 35.2 and 326.11 ± 360.2 min) or M (260.2 ± 150.2 and 599.6 ± 586.6 min). Proportion of time within desired interval of sedation score was comparable between groups. Morphine consumption during the 24 h following extubation was lower in group S than in groups P and M. Four hallucination episodes were reported in group P, five in group M, and none in group S (P=0.04). No hepatic or renal adverse events were reported. Mean plasma fluoride value was 82 μmol l(-1) (range 12-220 μmol l(-1)), and mean ambient sevoflurane concentration was 0.3 ± 0.1 ppm. Long-term inhaled sevoflurane sedation seems to be a safe and effective alternative to i.v. propofol or midazolam. It decreases wake-up and extubation times, and post extubation morphine consumption, and increases awakening quality.	AnaConDa device included.
Rohm 2009	The sedation time in the intensive care unit was comparable between the sevoflurane (9.2 +/- 4.3 h) and the propofol (9.3 +/- 4.7 h) group. Alpha-glutathione-s-transferase levels were significantly increased at 24 and 48 h postoperatively compared with preoperative values in both groups, without significant differences between the groups. N-acetyl-glucosaminidase and serum creatinine remained unchanged in both study groups, and urine output and creatinine clearance were comparable between the groups throughout the study period. Inorganic fluoride levels increased significantly (P	AnaConDa device included.

	< 0.001) at 24 h after sevoflurane exposure (39 +/- 25 micromol/L) compared with propofol (3 +/- 6 micromol/L) and remained elevated 48 h later (33 +/- 26 vs 3 +/- 5 micromol/L). One patient in each group suffered from renal insufficiency, requiring intensive diuretic therapy, but not dialysis, during hospital stay.	
Rohm 2008	Mean recovery times were significantly shorter with sevoflurane than with propofol (extubation time: 22 vs. 151 min; following commands: 7 vs. 42 min). The mean (SD) sevoflurane consumption was 3.2 +/- 1.4 mL/h to obtain mean endtidal concentrations of 0.76 vol%. No serious complications occurred during sedation with either sedative drug. The length of ICU stay was comparable in both groups, but hospital length of stay was significantly shorter in the sevoflurane group.	AnaConDa device included.
Turktan 2019	Demographic data, airway resistance, PEEP, frequency, TV, Ppeak and static pulmonary compliance values were similar between the groups. PaCO2 and end-tidal CO2 values were higher in Group S than in Group D. Sedation and patient comfort scores were similar between the two groups. Both sevoflurane and dexmedetomidine are suitable sedative agents in ICU patients with pulmonary diseases.	Conference abstract only. AnaConDa device included.
Meiser 2003	Emergence times were shorter (P<0.001) after desflurane than after propofol (25th, 50th and 75th percentiles): t(BIS75), 3.0, 4.5 and 5.8 vs 5.2, 7.7 and 10.3 min; time to first response, 3.7, 5.0 and 5.7 vs 6.9, 8.6 and 10.7 min; time to eyes open, 4.7, 5.7 and 8.0 vs 7.3, 10.5 and 20.8 min; time to squeeze hand, 5.1, 6.5 and 10.2 vs 9.2, 11.1 and 21.1 min; time to tracheal extubation, 5.8, 7.7 and 10.0 vs 9.7, 13.5 and 18.9 min; time to saying their birth date, 7.7, 10.5 and 15.5 vs 13.0, 19.4 and 31.8 min. Patients who received desflurane recalled significantly more of the five words. We did not observe major side-effects and there were no haemodynamic or laboratory changes except for a more marked increase in systolic blood pressure after stopping desflurane. Using a low fresh gas flow (air/oxygen 1 litre min(-1)), pure drug costs were lower for desflurane than for propofol (95 vs 171 Euros day(-1)). We found shorter and more predictable emergence times and quicker mental recovery after short-term postoperative sedation with desflurane compared with propofol. Desflurane allows precise timing of extubation, shortening the time during which the patient needs very close attention.	Study pre-dated AnaConDa.
Bellgardt 2019	A target-controlled, MAC-driven automated application of volatile anesthetics is technically feasible and enables an adequate depth of sedation. Gas consumption was highest for desflurane, which is also the most expensive volatile anesthetic. Although awakening times were shortest, the actual time saving of a few minutes might be negligible for most patients in the intensive care unit. Thus, using desflurane seems not rational from an economic perspective.	Study used the MIRUS™ (TIM, Koblenz, Germany) device, an electronical gas delivery system.

El 2016	Elderly individuals were more vulnerable for POCD. The time needed for patients to respond, extubate, restore clear mind after the end of sedation in the two groups there was statistical significance in favour of the inhalational group. Regarding incidence of POCD in the two groups there were lower absolute numbers in the inhalational group but no statistical significance. Aortic cross-clamp time had a significant effect on POCD. Hospital and ICU stay of POCD patients were significantly increased. Despite, the route of sedation did not affect the incidence of POCD; however, inhaling sevoflurane for sedation had the privilege of shorter time for patients to respond and to regain clear mind and shorter time for extubation from mechanical ventilation as well than intravenous sedation. Elderly patients have the highest risk for developing POCD, and they should be the targeted group for prophylactic treatment.	Conference abstract only. AnaConDa device included.
Guinot 2020	The primary endpoint was the kinetics of cTnI in the 48 hours after surgery. In terms of secondary outcomes, time to extubation was significantly (p=0.001) shorter among the sevoflurane sedated patients than propofol. Both sevoflurane and propofol groups were comparable (non-significant) regarding ICU stay, hospital stay, and mortality outcomes.	Added from SLR update (14th April 2021) MIRUS device
Daume 2021	The primary outcome was the time required to decrease the end-tidal concentration to 50%. Regarding the secondary outcomes, the desflurane group showed significantly shorter awakening time (p=0.007) and time to move all extremities (p=0.037) compared to isoflurane. However, in terms of other emergence outcomes like the movement of the first extremity, opening eyes, and squeezing a hand, the duration was comparable [non-significant (p=0.226, 0.071, 0.075)] between desflurane and isoflurane groups.	
Observational studies		
Staudacher 2018	Data on 214 patients were reported, 178 patients on propofol (and sufentanil) and 36 patients on isoflurane (and sufentanil). Median time to first spontaneous breathing (9.3 h vs. 9.5 h, p = 0.373), median duration on mechanical ventilation in extubated patients (99.4 h vs. 105.7 h, p = 0.692) and median ICU stay (11.1d vs. 9.8d, p = 0.320) were similar in patients on propofol or isoflurane, respectively. Findings were confirmed by propensity score matching. Opioid dose was significantly lower in the isoflurane group (p < 0.001) while noradrenaline dose was significantly higher (p = 0.004).	
Bellgardt 2016	After sedation with isoflurane, the in-hospital mortality and 365-day mortality were significantly lower than after propofol/midazolam sedation: 40 versus 63% (P = 0.005) and 50 versus 70% (P= 0.013), respectively. After adjustment for potential confounders (coronary heart disease, chronic obstructive pulmonary disease, acute renal failure, creatinine, age and Simplified Acute Physiology Score II), patients after	

	isoflurane were at a lower risk of death during their hospital stay (OR 0.35; 95% CI 0.18 to 0.68, P = 0.002) and within the first 365 days (OR 0.41; 95% CI 0.21 to 0.81, P = 0.010).	
Krannich 2017	A matched pairs analysis revealed that time on ventilator (difference of median, 98.5 hr; p = 0.003) and length of ICU stay (difference of median, 4.5 d; p = 0.006) were significantly shorter in patients sedated with isoflurane when compared with IV sedation.	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

SED001 **(Including Meiser et al., 2020 – first report at ESICM congress)**	
How are the findings relevant to the decision problem?	[redacted]
Does this evidence support any of the claimed benefits for the technology? If so, which?	[redacted]
Will any information from this study be used in the economic model?	yes
What are the limitations of this evidence?	Open-label design, blinding was only feasible at data analysis stage. Limited duration of randomisation period (48+/-6h). Statistical analyses design for non-inferiority on primary endpoint (sedation efficacy).
How was the study funded?	Sedana Medical sponsored study
Sackey et al. 2007	
How are the findings relevant to the decision problem?	PICO relevance: Twenty ventilator-dependent ICU patients aged 27 to 80 years were randomised to sedation with isoflurane via the AnaConDa® or intravenous midazolam. Helps to develop sedation measurement instruments for later trials including inhaled sedation. End-tidal isoflurane concentration appeared to be a better indicator of clinical sedation depth than BIS.
Does this evidence support any of the claimed benefits for the technology? If so, which?	no
Will any information from this study be used in the economic model?	no

What are the limitations of this evidence?	Clinical development of sedation measures not comparing outcomes between sedation regimens.
How was the study funded?	Supported in part by Hudson RCI (supplied the Anesthetic Conserving Devices) and Abbott Scandinavia (provided isoflurane) Supported by Department of Anaesthesiology and Intensive Care Medicine, Karolinska University Hospital Solna.
Hanafy 2005	
How are the findings relevant to the decision problem?	PICO relevance: Twenty-four patients scheduled for CABG were randomized to either isoflurane group (number= 12) which received isoflurane for postoperative sedation via AnaConDa to obtain an end tidal concentration of 0.5% or midazolam group (number= 12) which received midazolam as a conventional method of postoperative sedation in a dose of 0.02-0.05 mg/kg/h.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Wake-up times were significantly shorter in the isoflurane group where time to extubation [mean (SD)] was15.2 (5.3) min and in the midazolam group 120.1 (30.3) min, P value = 0. 01. Time to follow verbal command was 16.3 (3.2) min versus 60.4 (20.4) min for the isoflurane group and midazolam group, respectively, P value = 0.03. Patients in the isoflurane group were mobilized significantly earlier from bed 8 (1.8) h, compared to 14 (3.3) h in midazolam group, P value <0.05.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Small sample size. This study was limited by being not double-blind and it is possible that some bias affected the subjective assessment of sedation adequacy made by nursing staff.
How was the study funded?	Not provided
Sackey et al. 2004	
How are the findings relevant to the decision problem?	PICO relevance: Forty ventilator-dependent intensive care unit patients 18-80yrs old, expected to need >12 hrs sedation. Patients were randomized to sedation with inhaled isoflurane via AnaConDa or intravenous midazolam infusion.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Wake-up times were significantly shorter in the isoflurane group than in the control group (time to extubation [mean ±SD] 10 ± 5 vs. 252 ± 271 mins, time to follow verbal command 10± 88 vs. 110 ± 132 mins). Proportion of time within the desired sedation interval was comparable between groups (isoflurane 54%, midazolam 59% of sedation time).
Will any information from this study be used in the economic model?	no

What are the limitations of this evidence?	The nature of the study made double-blind design unfeasible, and it is possible that some bias affected the subjective assessment of sedation adequacy made by nursing staff. This study did not include patients with intracranial events; potential circulatory effects of isoflurane sedation in this group need to be studied. Clinically, no withdrawal or hallucinations were observed after sedation in the isoflurane group, but this was not systematically assessed. Short- and long-term psychological follow-up after prolonged isoflurane sedation is needed.
How was the study funded?	Supported in part by Hudson RCI (supplied the Anesthetic Conserving Devices) and Abbott Scandinavia (provided isoflurane)
Spencer et al. 1992	
How are the findings relevant to the decision problem?	PICO relevance: Sixty patients aged 17-80 years who required mechanical ventilation for more than 24 h. Interventions: Sedation with either 0.1-0.6% isoflurane in an air-oxygen mixture (30patients) or a continuous infusion of midazolam 0.02-0.20 mg/kg/h (30 patients).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Patients sedated with isoflurane recovered more rapidly and were weaned from mechanical ventilation sooner than those sedated with midazolam.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study pre-dates AnaConDa. Isoflurane was added continuously to the inspired air-oxygen mixture using a Siemens' isoflurane vaporizer 952 mounted distal to the oxygen/air blender on a Siemens-Elema Servo 900B ventilator.
How was the study funded?	Supported by Abbott Labs UK
Kong et al. 1989	
How are the findings relevant to the decision problem?	PICO relevance: Sedation with either 0-1-0-6% isoflurane in an air-oxygen mixture (30 patients) or a continuous intravenous infusion of midazolam 0-01-0-20 mg/kg/h (30 patients).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Isoflurane produced satisfactory sedation for a greater proportion of time (86%) than midazolam (64%), and patients sedated with isoflurane recovered more rapidly from sedation.
Will any information from this study be used in the economic model?	no

What are the limitations of this evidence?	Study pre-dates AnaConDa. Isoflurane was added to the air-oxygen mixture by a Siemens isoflurane vaporiser 952 (Siemens-Elema AB, Sweden).
How was the study funded?	NHS / University of Bristol
Walczak et al. 2019	
How are the findings relevant to the decision problem?	PICO relevance: This is a sub study of VALTS: a prospective randomized controlled trial (n=60 patients); expected to require mechanical ventilation >48hours, randomized (2:1) to receive either inhaled isoflurane volatile sedation via the AnaConDa device (n=40) or intravenous propofol and/or midazolam sedation (n=20).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. The use of volatile anaesthetics for sedation in critically ill patients may be associated with a lower incidence of delirium and lower proportion of patients with long-term cognitive impairment.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Based on congress abstract.
How was the study funded?	None
Jerath et al. 2015	
How are the findings relevant to the decision problem?	PICO relevance: One hundred forty-one patients undergoing coronary artery bypass graft surgery with normal or mildly reduced left ventricular systolic function. Intervention: Participants were randomly assigned to receive anaesthesia and postoperative sedation using IV propofol (n = 74) or inhaled volatile (isoflurane or sevoflurane) anaesthetic agent (n = 67) via AnaConDa.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Patients sedated using inhaled volatile agent displayed faster readiness to extubation time at 135 minutes (95–200min) compared with those receiving IV propofol at 215 minutes (150–280min) ($p < 0.001$). Extubation times were faster within the volatile group at 182 minutes (140–255min) in comparison with propofol group at 291 minutes (210–420min) ($p < 0.001$). The volatile group showed a higher prevalence of vasodilatation with hypotension and higher cardiac outputs necessitating greater use of vasoconstrictors.
Will any information from this study be used in the economic model?	no

What are the limitations of this evidence?	This sub-analysis was performed from a study originally powered to assess cardiac outcomes in patients receiving volatile-based preconditioning and postconditioning (volatile anaesthesia and ICU sedation). The sample size calculation did not include assessment of sedation and extubation outcomes. Despite identifying faster extubation times among patients sedated with volatile agents, we did not formally record the time difference between discontinuing sedation and extubation. We recognize this is a single-center open-label, evaluator-blinded trial that is subject to institutional practice bias. Blinding of the AnaConDa setup, scavenging, and end-tidal gas monitoring was considered logistically impossible.
How was the study funded?	none
Gomez et al. 1995	
How are the findings relevant to the decision problem?	PICO relevance: Forty consecutive, randomized patients undergoing cardiac surgery with ECC were studied prospectively. Patients were assigned to receive either isoflurane or propofol.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Statistically significant differences were found for stabilization of sedation time (4 min ± 1.17 for isoflurane and 11.7 min ± 4.78 for propofol) and time to endotracheal extubation (56,2 min ± 20.47 for isoflurane and 72,65 min ± 30.90 for propofol), number of times dosage had to be changed (2.20 ± 0.89 with isoflurane and 7.05 ± 2.58 with propofol) and time of administration had to be interrupted (8.45 min ± 8.73 with propofol and 0.75 min + 1.94 with isoflurane).
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study pre-dates AnaConDa. Isoflurane using an Ohmeda Portable Drawover Vaporizer.
How was the study funded?	None provided
Millane et al. 1992	
How are the findings relevant to the decision problem?	PICO relevance: A direct comparison between propofol and isoflurane. Twenty-four patients predicted to require artificial ventilation for at least 48h were entered into a randomised crossover study to monitor sedation quality and time to recovery from sedation.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No significant differences were detected between isoflurane and propofol in terms of sedation quality or time to recovery from sedation. Both agents appear to be safe, and few adverse events directly applicable to either agent occurred.

Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study pre-dated AnaConDa. Only seven of the 24 patients (17%), with a wide range of pathology, completed the study; nine patients died and eight were withdrawn. Studies in ICU are hampered by heterogeneity and high mortality, a point particularly relevant to a study which stipulated as an entry criterion that patients should be predicted to require artificial ventilation for at least 48 h. The study design attempted to avoid some of the bias arising from heterogeneity by randomising patients in two groups (medical and surgical) in a crossover fashion, and direct comparative analysis was limited to patients who completed the entire 48 h primary study period.
How was the study funded?	Abbott Labs provided vaporisers and drugs
Jabaudon et al. 2017	
How are the findings relevant to the decision problem?	PICO relevance: Adult patients were randomized within 24 hours of moderate-to-severe ARDS onset to receive either intravenous midazolam or inhaled sevoflurane for 48 hours.
Does this evidence support any of the claimed benefits for the technology? If so, which?	In patients with ARDS, use of inhaled sevoflurane improved oxygenation and decreased levels of a marker of epithelial injury and of some inflammatory markers, compared with midazolam.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	This was a single-center study by design and without double-blinded intervention. It was small, and only assessed minor outcomes (i.e., arterial oxygenation and levels of sRAGE and cytokines)
How was the study funded?	Supported by grants from the Auvergne Regional Council and the French Agence Nationale de la Recherche and the Direction Generale de l'Offre de Soins.
Marcos-Vidal et al. 2014	
How are the findings relevant to the decision problem?	PICO relevance: In the postoperative period patients were divided in two groups to receive sedation with either sevoflurane through the AnaConDa system or propofol. Data from 129 patients, 62 sedated with propofol and 67 with sevoflurane, were analyzed.
Does this evidence support any of the claimed benefits for the	The post-operative sedation with sevoflurane after cardiac surgery with cardiopulmonary bypass is a valid alternative to propofol. It does not increase the number of side effects related to kidney damage in patients with no prior renal disease, leading to reduced troponin T levels 12 and 48 hours after admission.

technology? If so, which?	
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	The study limitations include the sequential selection of patients, who were alternatively enrolled into each study group. A double-blind study was not conducted because of the characteristics of drugs administered for sedation; only the part related to statistical analysis was blinded.
How was the study funded?	None
Guerrero et al. 2013	
How are the findings relevant to the decision problem?	PICO relevance: a prospective trial with 60 patients undergoing coronary artery bypass graft surgery divided into 3 groups according to the administration of hypnotic drugs in the intraoperative and postoperative periods (sevoflurane, sevoflurane: SS, sevoflurane-propofol: SP, propofol-propofol: PP).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Sevoflurane administration in patients undergoing off-pump coronary artery bypass graft, in the operating room and the intensive care unit, decreases myocardial injury markers compared with patients who only received sevoflurane in the intraoperative period, but both were a better option to decrease levels of myocardial markers when compared with the propofol group.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study was not powered to evaluate major clinical outcomes. Study was only blinded with regard to data analysis.
How was the study funded?	None
Soro et al. 2012	
How are the findings relevant to the decision problem?	PICO relevance: Seventy-five adult patients were assigned randomly to receive anaesthesia and postoperative sedation either with propofol (control, n = 37) or sevoflurane (n = 36).
Does this evidence support any of the claimed benefits for the technology? If so, which?	In patients undergoing coronary bypass graft surgery, continuous administration of sevoflurane as a sedative in the ICU for at least 4h postoperatively did not yield significant improvements in the extent and time course of myocardial damage biomarkers compared to propofol.

Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	A first limitation of our study is that it was a single-centre study. Multicentre studies reduce the effect of the special characteristics of a single institution. Another limit of our study is the sample size. calculations were performed based on historical recordings in agreement with previous studies and not on a specific pilot study. Consequently, different reference values for TnI concentration could produce a different sample size and may leave our study underpowered.
How was the study funded?	None declared
Steurer et al. 2012	
How are the findings relevant to the decision problem?	After arrival in the intensive care unit (ICU), 117 patients were randomized to be sedated for at least 4 hours with either propofol or sevoflurane. Sevoflurane was administered by using the AnaConDa device. Fifty-six patients were analyzed in the propofol arm, and 46 patients in the sevoflurane arm.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Concentration of troponin T as the most sensitive marker for myocardial injury at POD1 was significantly lower in the sevoflurane group compared with the propofol group (unadjusted difference, -0.4; 95% CI, -0.7 to -0.1; P < 0.01; adjusted difference, -0.2; 95% CI, -0.4 to -0.02; P = 0.03, respectively). Late postconditioning with the volatile anaesthetic sevoflurane might mediate cardiac protection, even with a late, brief, and low-dose application.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Initial propofol use in both groups. Postconditioning phase was relatively short (4 hours).
How was the study funded?	This study was supported with a research grant from Abbott AG, Baar, Switzerland.
Hallström et al. 2012	
How are the findings relevant to the decision problem?	PICO relevance: Following coronary artery bypass surgery with cardiopulmonary bypass, 100 patients were randomized to sedation with sevoflurane via the AnaConDa device or propofol.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Sevoflurane sedation after cardiac surgery leads to shorter wake-up times and quicker cooperation compared to propofol. No differences were seen in ICU-stay, adverse memories or recovery events in our short-term sedation.

Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	The study was not double-blinded, due to practical reasons with the new sevoflurane delivery device. There are different traditions of dosing propofol following cardiac surgery, and our propofol starting dose might have been higher than in some other units, potentially affecting wake-up times. The loss to follow-up in the ICU Memory Tool test could possibly have been reduced with an additional follow-up after hospital discharge. Finally, while we classified patients as agitated only if they required treatment for agitation, we did not use a validated delirium instrument.
How was the study funded?	Abbott Scandinavia AB sponsored purchase of sevoflurane (Sevorane ®) and Sedana Medical AB supplied the anesthetic conserving device (AnaConDa ®).
Mesnil et al. 2011	
How are the findings relevant to the decision problem?	PICO relevance: Sixty intensive care unit (ICU) patients expected to require more than 24 h sedation were randomly assigned to one of three groups: group S, inhaled sevoflurane; group P, IV propofol; group M, IV midazolam. Sevoflurane was administered via the AnaConDa.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, long-term inhaled sevoflurane sedation (via AnaConDa) seems to be a safe and effective alternative to IV propofol or midazolam. It decreases wake-up and extubation times, and post extubation morphine consumption, and increases awakening quality.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	A double-blind design was not applicable to our study, so we cannot ignore that bias could have affected the subjective assessment of the nursing staff. The studied population is young and mainly post trauma, so our results should be applied with caution to a larger population.
How was the study funded?	Support was provided only from institutional sources.
Rohm et al. 2009	
How are the findings relevant to the decision problem?	PICO relevance: after major abdominal, vascular or thoracic surgery 125 patients were allocated to receive either sevoflurane (n = 64) via the AnaConDa (end-tidal 0.5–1 vol%) or IV propofol (n= 61) for postoperative sedation up to 24 h.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Short-term sedation with either sevoflurane using AnaConDa or propofol did not negatively affect renal function postoperatively.

Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	A double-blind study design was not feasible.
How was the study funded?	None provided
Rohm et al. 2008	
How are the findings relevant to the decision problem?	PICO relevance: A total of 70 patients after elective coronary artery bypass graft surgery either received sevoflurane via AnaConDa (n = 35) or propofol (n = 35) for short-term postoperative sedation in the ICU.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Mean recovery times were significantly shorter with sevoflurane than with propofol (extubation time: 22 vs. 151 min; following commands: 7 vs. 42 min). The length of ICU stay was comparable in both groups, but hospital length of stay was significantly shorter in the sevoflurane group.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Short-term duration and small sample size.
How was the study funded?	The present study was an investigator-initiated trial granted by the hospital and department sources of the Klinikum Ludwigshafen, Germany.
Turktan et al. 2019	
How are the findings relevant to the decision problem?	PICO relevance: 30 patients with an American Society of Anesthesiologist status I-III, who were mechanically ventilated, who had pulmonary disorders and who needed sedation were included in the study. Patients were divided into two groups for sedation, 0.5%-1% sevoflurane (4-10 mL h−1) was used by an AnaConDa Device in Group S (n=15), and iv dexmedetomidine infusion (1 µg−1 kg−1 10 min−1 loading and 0.2-0.7 µg−1 kg−1 h−1 maintenance) was performed in Group D (n=15).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Demographic data, airway resistance, PEEP, frequency, TV, Ppeak and static pulmonary compliance values were similar between the groups. PaCO2 and end-tidal CO2 values were higher in Group S than in Group D. Sedation and patient comfort scores were similar between the two groups. Conclusion: Both sevoflurane and dexmedetomidine are suitable sedative agents in ICU patients with pulmonary diseases.

Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	The study did not evaluate blood sevoflurane and dexmedetomidine concentrations due to high costs. Second, the number of patients participating in the study (n=30) was insufficient. However, the number of patients requiring sedation in the ICUs within the period of the study was 30. Therefore, the study was presented as a preliminary study. Third, we did not measure the concentration of sevoflurane in the ICU because we did not have enough equipment to evaluate.
How was the study funded?	None
Meiser et al. 2003	
How are the findings relevant to the decision problem?	Sixty patients after major operations were allocated randomly to receive either desflurane or propofol. All patients were receiving mechanical ventilation of the lungs.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Shorter and more predictable emergence times and quicker mental recovery after short-term postoperative sedation with desflurane compared with propofol. Desflurane allows precise timing of extubation, shortening the time during which the patient needs very close attention.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study pre-dates AnaConDa. Desflurane using modified TEC-6 vaporizer.
How was the study funded?	The study was supported in part by an unrestricted research grant from Baxter, Erlangen, Germany. Baxter also paid costs directly linked to the study (patient insurance, study drugs, additional laboratory tests and travel expenses). The Cicero anaesthesia ventilator was kindly provided by Drager Medical, Lubeck, Germany.
Bellgardt et al. 2019	
How are the findings relevant to the decision problem?	Mechanically ventilated and sedated patients after major surgery were enrolled. Upon arrival in the intensive care unit, patients obtained intravenous propofol sedation for at least 1 h to collect ventilation and blood gas parameters, before they were switched to inhalational sedation using MIRUS™ device with isoflurane, sevoflurane, or desflurane.
Does this evidence support any of the claimed benefits for the	A target-controlled, MAC-driven automated application of volatile anaesthetics is technically feasible and enables an adequate depth of sedation. Gas consumption was highest for desflurane, which is also the most expensive volatile anaesthetic. Although awakening times were shortest, the actual time saving of a few minutes might be negligible for

technology? If so, which?	most patients in the intensive care unit. Thus, using desflurane seems not rational from an economic perspective.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	This study lacks a common intravenous control group, which is a limitation.
How was the study funded?	Departmental funding only.
El Shora et al. 2016	
How are the findings relevant to the decision problem?	Sixty adult patients scheduled for elective cardiac surgery were enrolled. On arrival in the ICU, sedation was provided by either inhalational route or intravenous route.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Elderly individuals were more vulnerable for postoperative cognitive dysfunction (POCD). The time needed for patients to respond, extubate, restore clear mind after the end of sedation in the two groups there was statistically significant in favour of the inhalational group. Regarding incidence of POCD in the two groups there were lower absolute numbers in the inhalational group but no statistical significance. Aortic cross-clamp time had a significant effect on POCD. Hospital and ICU stay of POCD patients were significantly increased.
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Congress abstract only.
How was the study funded?	None provided
Daume et al., 2021 (added in SLR update)	
How are the findings relevant to the decision problem?	PICO relevance: Twenty-one consecutive critically ill patients were alternately allocated to the two study groups, obtaining inhaled sedation with either desflurane or isoflurane. After 24 h study sedation, anesthetic washout curves were recorded, and a standardized wake-up test was performed.
Does this evidence support any of the claimed benefits for the	no

technology? If so, which?	
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Not blinded. Alternate allocation (not randomised). Patient group only very severely ill.
How was the study funded?	The study was performed without third party funding. Two MIRUS™ control units, one each for desflurane, and isoflurane, together with the necessary disposables were supplied by Pall Corporation, Dreieich, Germany
Guinot et al., 2020 (added in SLR update)	
How are the findings relevant to the decision problem?	PICO relevance: Adult patients (n=81) undergoing cardiac surgery were randomised 1:1 to inhaled sevoflurane using the MIRUS system or intravenous infusion of propofol.
Does this evidence support any of the claimed benefits for the technology? If so, which?	no
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Blinding. Small sample size.
How was the study funded?	Institutional funding only.
Staudacher et al. 2018	
How are the findings relevant to the decision problem?	PICO relevance: compared time to spontaneous breathing and time on mechanical ventilation after cardiac arrest and cardiopulmonary resuscitation in patients sedated with isoflurane plus sufentanil, with patients sedated with propofol plus sufentanil during targeted temperature management.
Does this evidence support any of the claimed benefits	Time to spontaneous breathing and ICU stay was shorter for isoflurane patients, but this did not show statistical significance.

for the technology? If so, which?	
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study design: Single centre retrospective registry case analysis using propensity score matching.
How was the study funded?	
Bellgardt et al. 2016	
How are the findings relevant to the decision problem?	PICO relevance: compared mortality after sedation with either isoflurane or propofol/midazolam among consecutive cohort of 369 critically ill surgical patients defined within the database of the hospital information system. All patients were continuously ventilated and sedated for more than 96h.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients after isoflurane were at a lower risk of death during their hospital stay (OR 0.35; 95% CI 0.18 to 0.68, P = 0.002) and within the first 365 days (OR 0.41; 95% CI 0.21 to 0.81, P = 0.010).
Will any information from this study be used in the economic model?	no
What are the limitations of this evidence?	Study design: retrospective analysis of data in a hospital database for a cohort of consecutive patients.
How was the study funded?	
Krannich et al. 2017	
How are the findings relevant to the decision problem?	PICO relevance: mechanically ventilated ICU patients sedated with isoflurane via AnaConDa were compared with standard IV sedation (midazolam).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Time on ventilator (difference of median, 98.5 hr; p = 0.003) and length of ICU stay (difference of median, 4.5 d; p = 0.006) were significantly shorter in patients sedated with isoflurane when compared with IV sedation.

Will any information from this study be used in the economic model?	Yes (for real-world comparison to midazolam)
What are the limitations of this evidence?	Study design: Observational analysis of clinical data at single (university) centre.
How was the study funded?	

6 Adverse events

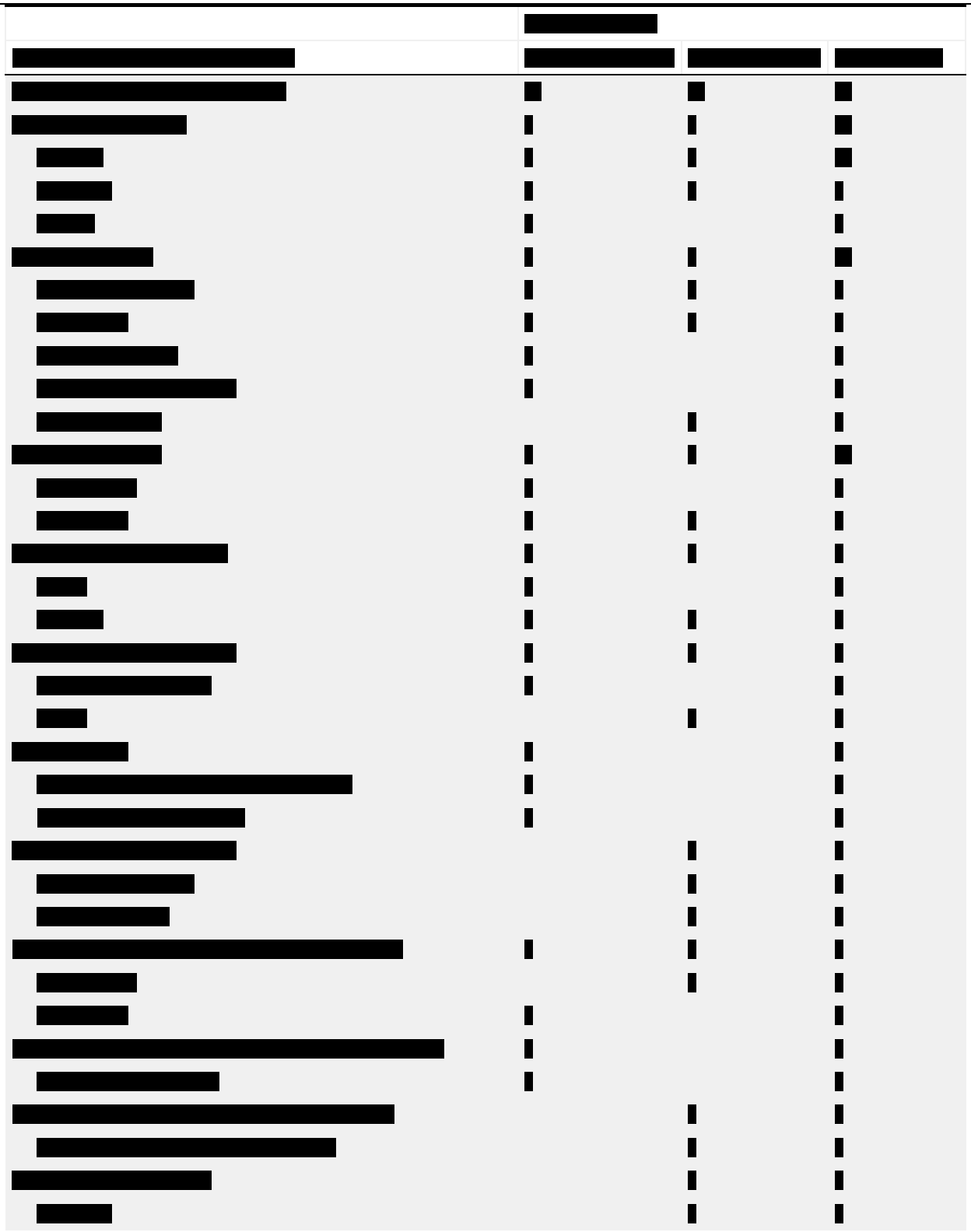
Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

n/a

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

[redacted]

Table 7: Summary of treatment emergent AEs causally related to treatment by descending frequency (Safety Population, SED001 CSR, data on file.)



In the SLR a total of 13 studies reported safety and tolerability data. All studies except one (Meiser et al. 2003) utilised AnaConDa for sedation with inhalational agents. Nine studies assessed sevoflurane, two assessed isoflurane, and one study each assessed isoflurane/sevoflurane, desflurane. A summary of safety and tolerability data identified in the SLR is provide in Table 8.

Table 8: Safety and tolerability data reported among the SLR included studies

Study name (Trial name)	Treatment	N	Any adverse event n (%)	Agitation n (%)	Hypotension n (%)	Reintubation n (%)	Respiratory depression n (%)	Nausea/ vomiting n (%)	Shivering n (%)	All-cause treatment withdrawals n (%)
Hanafy 2005	Isoflurane using ACD	12	-	1 (8)	1 (8)	0 (0)	-	-	-	-
	Midazolam	12	-	1 (8)	1 (8)	0 (0)	-	-	-	-
Sackey 2004	Isoflurane using ACD	20	5 (25)*	4 (20)	3 (15)	-	-	-	-	2/20 (10)
	Midazolam	20	6 (30)*	3 (15)	2 (10)	-	-	-	-	2/20 (10)
Jerath 2015	Isoflurane or Sevoflurane using ACD	67	-	-	-	-	-	11 (16.42)	6 (8.96)	12/79 (15.19)
	Propofol	74	-	-	-	-	-	6 (8.11)	9 (12.16)	4/78 (5.13)
Jabaudon 2017 (SEGA)	Sevoflurane using ACD	25	-	-	-	-	-	-	-	0/25 (0)
	Midazolam	25	-	-	-	-	-	-	-	0/25 (0)
Marcos-Vidal 2014	Sevoflurane using ACD	72	-	-	-	-	-	-	-	5/72 (6.94)
	Propofol	72	-	-	-	-	-	-	-	10/72 (13.89)
Soro 2012	Sevoflurane using ACD	36	-	-	-	-	-	-	-	0/36 (0)
	Propofol	39	-	-	-	-	-	-	-	2/39 (5.13)
Steurer 2012	Sevoflurane using ACD	46	-	-	-	-	-	OR (Adj): 1.3 Unadj: 1.4	-	11/57 (19.3)
	Propofol	56	-	-	-	-	-	1 (reference)	-	4/60 (6.67)
Hellstrom 2012	Sevoflurane using ACD	49	-	1 (2.04)	-	-	-	12 (24.49)	2 (4.08)	7/50 (14)
	Propofol	50	-	0 (0)	-	-	-	9 (18)	1 (2)	4/50 (8)
Mesnil 2011	Sevoflurane using ACD	19	-	-	-	0 (0)	-	-	-	1/20 (5)
	Propofol	14	-	-	-	1 (7.14)	-	-	-	6/20 (30)
	Midazolam	14	-	-	-	3 (21.43)	-	-	-	6/20 (30)
Rohm 2009	Sevoflurane using ACD	64	-	3 (4.5)	-	0 (0)	-	6 (9.4)	-	1/65 (1.54)
	Propofol	61	-	1 (1.6)	-	2 (3.08)	-	4 (6.6)	-	4/65 (6.15)
Rohm 2008	Sevoflurane using ACD	35	-	-	-	-	2 (5.71)	4 (11.43)	16 (45.72)	-
	Propofol	35	-	-	-	-	2 (5.71)	6 (17.14)	10 (28.57)	-
Turktan 2019	Sevoflurane using ACD	15	-	-	-	-	0 (0)	-	-	-
	Dexmedetomidine	15	-	-	-	-	0 (0)	-	-	-
Meiser 2003	Desflurane using modified TEC-6 vaporizer	25	-	2 (8)	-	-	-	0 (0)	-	3/30 (10)
	Propofol	28	-	4 (14.29)	-	-	-	2 (7.14)	-	1/30 (3.33)

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

A meta-analysis pooling the SED001 RCT and the 22 RCTs identified in the SLR is planned following publication of the SED001 clinical study itself (late 2021). Meantime the objective of the SLR is to provide a narrative summary of the efficacy, safety, and tolerability evidence for inhalational versus intravenous sedatives among mechanically ventilated adult patients in ICU alongside the CSR-SED001 study results, this is provided in the qualitative review section below.

Four earlier published SLRs report the meta-analysis results for comparison of inhalational and intravenous agents. Three SLRs were published in 2017, whereas one was published in 2016 timeframe.

Jerath et al. 2017 compared inhalational sedatives with intravenous propofol and midazolam among ventilated critical care patients. The review included 12 randomised controlled trials from 15 publications ranged from 1989 to 2015. The review followed the methodology described by the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias assessment was performed using the Cochrane risk of bias tool. The included studies were analysed using fixed and random effect models based on heterogeneity assessment. The authors compared the entire class of inhalational versus intravenous agents.

Spence et al. 2017 reported the efficacy and safety of inhaled anaesthetics for postoperative sedation during mechanical ventilation in adult cardiac surgery patients. The review included eight randomised controlled trials from nine publications ranged from 1995 to 2015. The review followed PRISMA guidelines. The risk of bias assessment was performed using the Cochrane risk of bias tool. The authors performed statistical analyses using RevMan 5.3 statistical software for meta-analysis. Among eight studies, isoflurane or sevoflurane were compared with propofol in seven studies, and with midazolam in one study.

Kim et al. 2017 conducted a systematic review and meta-analysis comparing the effects of inhalational and intravenous sedation in adult ICU patients. The review included 13 randomised controlled trials (12 trials after linking) from 13 publications ranged from 2004 to 2015. The review followed PRISMA guidelines. The risk of bias assessment was performed using the Cochrane risk of bias tool. The authors performed statistical analyses

using the meta-analysis package for R software. All included studies used AnaConDa for inhalational sedation.

Landoni et al. 2016 conducted a systematic review and meta-analysis of randomised clinical trials assessing inhalational agents in the medical and surgical ICU. The review included 12 randomised controlled trials from 15 publications ranged from 1989 to 2015. The review followed the methodology described by the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA guidelines. The risk of bias assessment was performed using the Cochrane risk of bias tool. The authors performed statistical analyses using RevMan 5.2 statistical software for meta-analysis.

Report all relevant results, including diagrams if appropriate.

The Jerath et al. 2017 meta-analysis results indicated benefit with inhalational sedatives in reducing extubation time versus intravenous agents. The reductions were specifically higher against midazolam. The duration of mechanical ventilation also significantly favoured inhalational sedatives (p=0.03). The inhalational and intravenous agents remained comparable among all other analysed outcomes i.e. time to obey verbal commands, the proportion of time spent in target sedation, adverse events, death, or length of hospital stay.

In the study by Spence et al. 2017, times to extubation after intensive care admission or stopping sedation were less in patients sedated using inhalational anaesthetics. There was no difference was found in the length of intensive care unit or hospital stay. Patients sedated with inhalational anaesthetic had lower troponin concentrations compared with patients given intravenous sedation, potentially suggesting reduced cardiac damage.

Kim et al. 2017 found that inhalational sedation shortened the awakening time and extubation time as compared with intravenous sedation. The authors reported no differences in the lengths of ICU and hospital stay between the two groups. Patients sedated with inhalational sedatives showed lower serum troponin levels after ICU admission than patients who received intravenous sedation.

The Landoni et al. 2016 meta-analysis results indicated reduced the time to extubation. The results for time to extubation were confirmed in all sub analyses (e.g. medical, and

surgical patients) and sensitivity analyses. No differences in length of hospital stay, ICU stay, and mortality was recorded.

Explain the main findings and conclusions drawn from the evidence synthesis.

Studies included in the 4 meta-analyses reported above were largely small and of short duration but clearly show reduced time to extubation and wake-up associated with inhalational sedatives when compared with standard-of-care IV sedatives (propofol, midazolam). These studies were not designed or powered to show differences in hospital efficiency metrics such as ICU and hospital length of stay, hence the pooling of these smaller studies tends to show comparable outcomes only. The recommendations for the next steps in these studies include the assessment of inhalational agents in larger multicentred trials as this evidence is mainly from the single centre trials.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

The SLR was undertaken to assess the efficacy and safety of inhalational sedatives compared with intravenous sedatives among mechanically ventilated patients. The published evidence for the SLR was searched from database inception to 3rd August 2020 for the studies that provide evidence on efficacy and safety of inhalational and intravenous sedatives in a randomised setting to develop a narrative synthesis of the findings according to PRISMA recommendations. A total of 22 studies published in 31 publications were included in the clinical SLR. Among these, 10 studies assessed sevoflurane, nine assessed isoflurane, and one study each assessed desflurane, sevoflurane/isoflurane, and unspecified volatile agent. In total 21 studies were published in the English language only, while one study was published in Spanish (Gomez et al. 1995).

Among 22 included studies, 15 used AnaConDa, 6 studies pre-dated AnaConDa (using Siemens vaporiser 952, Mark 3 Isotec vaporizer, Ohmeda portable drawover vaporizer, and TEC-6 vaporizer), and one study (Bellgardt et al. 2019) used the electronic MIRUS device

for the administration of inhalational agents among mechanically ventilated adults for sedation. In total, 18 studies were conducted in Europe, and two studies each were conducted in North America and Africa. Further, most of the included studies were conducted in a single centre (n=21) setting and were open-label (n=8) or single-blind (n=7) in design. Only two studies used adequate double-blind design (Kong et al.1989; Soro et al. 2012), while other trials cited disease area and procedural complexities for the use of single-blind or open-label design. Among the included studies, 12 studies included surgical patients (cardiac=10), nine included ICU admitted patients (multiple indications), and one included patients with ARDS (Jabaudon et al. 2017).

Provided here is a narrative review of results from the SLR for five key outcomes included in the decision problem, supplemented with results from the (unpublished) SED001 RCT.

Outcome (c) in decision problem: Sedation efficacy

Among the mechanically ventilated patients, statistically significant results were achieved in favour of inhalational sedatives (isoflurane, sevoflurane, and desflurane) versus intravenous agents (propofol and midazolam) for time to extubation outcome (Table 9). Isoflurane, sevoflurane, and desflurane were associated with significantly quicker extubation after the termination of sedation as compared to propofol and midazolam among all studies.

Table 9: Time to extubation reported among the included studies

Study name	Treatment	N	Mean/Median* (As reported)	SD/IQR*/Range**	Mean/Median* (Minutes)	SD/IQR*/Range**	p vs. Control
Hanafy 2005	Isoflurane using ACD	12	15.2 m	5.3	15.2	5.3	0.01
	Midazolam	12	120.1 m	30.3	120.1	30.3	
Sackey 2004	Isoflurane using ACD	20	10 m	5	10	5	0.001
	Midazolam	20	250 m	270	250	270	
Spencer 1992	Isoflurane using Siemens vaporiser 952	22	0.9* h	0.2-70**	54*	12-4200**	<0.001
	Midazolam	24	15* h	1.3-223**	900*	78-13380**	
Kong 1989	Isoflurane using Siemens vaporiser 952	14	60* m	30-135**	60*	30-135**	0.0016
	Midazolam	13	195* m	50-1080**	195*	50-1080**	
Jerath 2015	Isoflurane or Sevoflurane using ACD	67	182* m	140-255*	182*	140-255*	<0.001
	Propofol	74	292* m	210-420*	292*	210-420*	
Jerath 2015 Readiness to extubation time	Isoflurane or Sevoflurane using ACD	67	135* m	95-200*	135*	95-200*	<0.001
	Propofol	74	215* m	150-280*	215*	150-280*	

Gomez 1995	Isoflurane using Ohmeda Portable Drawover Vaporizer	20	56.2 m	20.47 20-120**	56.2	20.47 20-120**	0.047
	Propofol	20	72.65 m	30.9 28-150**	72.65	30.9 28-150**	
Steurer 2012	Sevoflurane using ACD[c]	45	444 m	222	444	222	-
	Propofol[c]	56	1022 m	3078	1022	3078	
Hellstrom 2012	Sevoflurane using ACD	49	10* m	10-100*	10*	10-100*	<0.001
	Propofol	50	25* m	21-240*	25*	21-240*	
Mesnil 2011	Sevoflurane using ACD	19	33.6 m	13.1	33.6	13.1	<0.001
	Propofol	14	326.11 m	360.2	326.11	360.2	
	Midazolam	14	599.62 m	586.95	599.62	586.95	
Rohm 2008	Sevoflurane using ACD	35	21.5* m	8-46*	21.5*	8-46*	<0.001
	Propofol	35	150.5* m	69-299*	150.5*	69-299*	
Meiser 2003	Desflurane using modified TEC-6 vaporizer	28	7.7* m	5.8-10.0* 4.5-17.0**	7.7*	5.8-10.0* 4.5-17.0**	<0.001
	Propofol	28	13.5* m	9.7-18.9* 4.75-102.0**	13.5*	9.7-18.9* 4.75-102.0**	
Bellgardt 2019	Isoflurane using MIRUS	10	10:10* m	8:00-20:30*	10.17*	8.0-20.5*	0.007
	Sevoflurane using MIRUS	10	7:30* m	4:37-14:22*	7.50*	4.62-14.37*	0.007
	Desflurane using MIRUS	10	3:00* m	3:00-6:00*	3.0*	3.0-6.0*	

ACD: Anaesthetic Conserving Device; d: Days; h: Hours; IQR: Interquartile range; m: Minute; N: Number of patients; SD: Standard deviation; cData taken from Spence 2017 meta-analysis sourced from authors; coloured cells specify calculated data to present results in the same unit of time i.e. minutes

In terms of the target sedation range most of the studies either did not report any significance level details or reported comparable (non-significant) time spent in the target sedation range by inhalational and intravenous agents. One study (Kong et al. 1989) achieving statistical significance levels regarding % of time spent in the target sedation range, indicated an advantage for isoflurane as compared to propofol.

In ***SED001 RCT*** the proportion of time at the desired sedation depth (primary endpoint) in isoflurane-treated patients, using the AnaConDa 50 mL or 100 mL administration system, was non-inferior to that of patients given propofol (difference in proportions isoflurane versus propofol mean 0.452%, 95% CI 2.996 to 2.093). Patients were at the desired sedation depth for a mean (SD) proportion of time of 92.8% (12.4) and 93.1% (12.4) for isoflurane and propofol, respectively. A statistical analysis of time to extubation based on Cox regression showed no difference in time to extubation between the two treatment groups. In a Mixed effect model where opiate intensity was evaluated and adjusted for BPS score, opiate intensity was significantly lower in the isoflurane group compared to the propofol group during day 1 and for the overall sedation period.

Outcomes (a, b) in decision problem: Wake-up times & Cognitive recovery

Inhalational agents were also associated with statistically significantly shorter emergence/wake-up/awakening times compared with propofol and midazolam in all eight studies reporting these endpoints (Table 10). Overall, the patients sedated with inhalational agents opened eyes and followed commands quickly after extubation. Some studies also associated pleasant awakening (Meiser et al. 2003) or better awakening quality (Mesnil et al. 2011) with inhalational agents along with lesser episodes of hallucinations and delusions (Mesnil et al. 2011; Sackey et al. 2004) compared to propofol. In line with time to emergence outcome, desflurane sedated patients remembered significantly more words in a five-word memory test as compared to propofol at all intervals (Mesnil et al. 2011).

Table 10: Wake-up/ Time to emergence reported among the included studies

Study name	Emergence type	Treatment	N	Mean/Median* (As reported)	SD/IQR*/ Range**	Mean/Median* (Minutes)	SD/IQR*/ Range**	p vs. Control
Hanafy 2005	Time to obey verbal commands (Wake-up time)	Isoflurane using ACD	12	16.3 m	3.2	16.3	3.2	0.03
		Midazolam	12	60.4 m	20.4	60.4	20.4	
Sackey 2004		Isoflurane using ACD	20	10 m	8	10	8	0.003
		Midazolam	20	110 m	130	110	130	
Spencer 1992		Isoflurane using Siemens vaporiser 952	22	10* m	5-180**	10*	5-180**	<0.001
		Midazolam	24	90* m	10-3780**	90*	10-3780**	
Kong 1989		Isoflurane using Siemens vaporiser 952	29	0* m	0-10**	0*	0-10**	0.0167
		Midazolam	27	0* m	0-300**	0*	0-300**	
Mesnil 2011		Sevoflurane using ACD	19	18.6 m	11.8	18.6	11.8	<0.001
		Propofol	14	91.3 m	35.2	91.3	35.2	
		Midazolam	14	260.2 m	150.5	260.2	150.5	
Meiser 2003		Desflurane using modified TEC-6 vaporizer	28	5* m	1.8-11/3.7-5.7*	5*	1.8-11/3.7-5.7*	<0.001
		Propofol	28	8.6* m	2.7-25/6.9-10.7*	8.6*	2.7-25/6.9-10.7*	
Bellgardt 2019		Isoflurane using MIRUS	10	20:22 m	21:20	20.37	21.33	0.004
		Sevoflurane using MIRUS	10	08:22 m	09:42	8.37	9.7	
		Desflurane using MIRUS	10	03:37 m	02:47	3.62	2.78	0.004

Meiser 2003	Open eyes	Desflurane using modified TEC-6 vaporizer	28	5.7* m	4.7-8.0*	5.7*	4.7-8.0*	<0.001
		Propofol	28	10.5* m	7.3-20.8*	10.5*	7.3-20.8*	
Bellgardt 2019		Isoflurane using MIRUS	10	15:48 m	18:05	15.8	18.08	0.017
		Sevoflurane using MIRUS	10	06:11 m	09:09	6.18	9.15	
		Desflurane using MIRUS	10	04:48 m	06:36	4.8	6.6	0.017
Rohm 2008	Eye opening; following commands, and hand grips	Sevoflurane using ACD	35	-	-	-	-	<0.002
		Propofol	35	-	-	-	-	
Spencer 1992	Writing home address	Isoflurane using Siemens vaporiser 952	22	1* h	0.2-71**	60*	12-4260**	<0.001
		Midazolam	24	21* h	2-72**	1260*	120-4320**	
Kong 1989		Isoflurane using Siemens vaporiser 952	16	58* m	20-270**	58*	20-270**	0.0001
		Midazolam	12	275* m	75-1440**	275*	75-1440**	
Spencer 1992	Spontaneous ventilation	Isoflurane using Siemens vaporiser 952	22	0.25* h	0.1-1**	15*	6-60**	<0.001
		Midazolam	24	3* h	0.17-42**	180*	10.2-2520**	
Meiser 2003	Squeeze hand	Desflurane using modified TEC-6 vaporizer	28	6.5* m	5.1-10.2*	6.5*	5.1-10.2*	<0.001
		Propofol	28	11.1* m	9.2-21.1*	11.1*	9.2-21.1*	
Meiser 2003	Telling birth date	Desflurane using modified TEC-6 vaporizer	28	10.5* m	7.7-15.5*	10.5*	7.7-15.5*	<0.001
		Propofol	28	19.4* m	13.0-31.8*	19.4*	13.0-31.8*	
Bellgardt 2019		Isoflurane using MIRUS	10	34:42 m	39:27	34.7	39.45	0.008; 0.021
		Sevoflurane using MIRUS	10	14:28 m	18:02	14.47	18.03	0.021
		Desflurane using MIRUS	10	05:37 m	02:17	5.62	2.28	0.008

ACD: Anaesthetic Conserving Device; TEC 6 V: modified TEC-6 vaporizer; h: Hours; IQR: Interquartile range; m: Minute; N: Number of patients; SD: Standard deviation

Studies reporting data for the proportion of patients with cognitive impairment or hallucinations indicated benefit with inhalational sedatives as compared to intravenous agents (Walczak 2019; El Shora 2016; Mesnil 2011, Sackey 2004, 2008). Inhalational agents were associated with a numerically lower percentage of delirium than intravenous agents, however, the difference did not reach the statistical significance level.

In **SED001 RCT** at 48 hours (study end), the Wake-up test was successful for 77% and 65% of patients in the isoflurane and propofol arm, respectively, with a median time to wake-up of 20.0 vs. 30.0 minutes. The difference tested in a Cox regression model adjusting for covariates age, BMI and RASS at sedation stop was highly significant, p=0.001.

Outcome (j) in decision problem: Duration of mechanical ventilation

Among five studies reporting ventilator duration, two studies (Rohm 2008, Rohm 2009) showed significantly shorter ventilator duration with inhalational versus intravenous sedatives, whereas three studies numerically favoured inhalational sedatives, but the differences did not reach statistical significance (Table 11).

Table 11: Duration of mechanical ventilation reported among the included studies

Study name (Trial name)	Treatment	N	Mean/Median* (As reported)	SD/IQR*	Mean/Median* (Hours)	SD/IQR*	p vs. Control
Jabaudon 2017 (SEGA)	Sevoflurane using ACD	25	12.5* d	5.8-17.3*	300.0*	139.2-415.2*	0.300
	Midazolam	25	17.0* d	6.0-30.0*	408.0*	144.0-720.0*	
Jabaudon 2017 (SEGA): controlled ventilation	Sevoflurane using ACD	25	2.5* d	2.0-6.0*	60.0*	48.0-144.0*	0.300
	Midazolam	25	4.0 d	2.0-10.3*	96.0*	48.0-247.2*	
Hellstrom 2012	Sevoflurane using ACD	49	185.0* m	74.0-230.0*	3.1*	1.2-3.8*	0.056
	Propofol	50	215.0* m	108.0-1056.0*	3.6*	1.8-17.6*	
Mesnil 2011	Sevoflurane using ACD	19	51.0* h	44.0-74.0*	51.0*	44.0-74.0*	0.453
	Propofol	14	61.0* h	41.0-66.5*	61.0*	41.0-66.5*	
	Midazolam	14	58.0* h	52.0-74.0*	58.0*	52.0-74.0*	
Rohm 2009	Sevoflurane using ACD	64	10.2 h	4.5	10.2	4.5	<0.009
	Propofol	61	13.0 h	5.7	13.0	5.7	
Rohm 2008	Sevoflurane using ACD	35	9.0 h	4.0	9.0	4.0	0.0001
	Propofol	35	12.5 h	5.8	12.5	5.8	

ACD: Anaesthetic Conserving Device; N: Number of patients; d: Days; h: Hours; m: Minute; coloured cells specify calculated data to present results in the same unit of time i.e. hours

In the **SED001 RCT** mean time on a ventilator (post-hoc analysis excluding patients switching sedation during 30day follow-up) was lower for isoflurane patients compared to propofol patients but did reach statistical significance (9.49 days vs. 11.87 days, p=0.211). When excluding deaths from this analysis (16 in isoflurane arm, 20 in propofol arm) the difference in time of a ventilator was bigger and statistically significant (3.65 days vs. 8.07 days, p=0.002).

Outcome (k) in decision problem: Length of stay in ICU

Within the SLR, 12 RCT studies reported on length of stay in ICU. The duration of ICU stay was found to be comparable between inhalational and intravenous sedatives in all 12 studies; however inhalational agents were associated with numerically shorter length of ICU stay (non-significant) (Table 12).

Table 12: Length of ICU stay reported among the included studies

Study name (Trial name)	Treatment	N	Mean/ Median* (As reported)	SD/IQR* /95%CI**/ Range#	Mean/ Median* (Hours)	SD/IQR* /95%CI**/ Range#	p vs. Control
Hanafy 2005	Isoflurane using ACD	12	19.0 h	4.5	19.0	4.5	NS
	Midazolam	12	20.0 h	3.6	20.0	3.6	
Sackey 2004[b]	Isoflurane using ACD	10	160.2 h	183.11	160.2	183.11	-
	Midazolam	7	188.4 h	181.34	188.43	181.34	
Spencer 1992	Isoflurane using Siemens vaporiser 952	30	48.5* h	4-600#	48.5*	4-600#	NS
	Midazolam	30	50* h	7-129#	50*	7-129#	
Jerath 2015	Isoflurane or Sevoflurane using ACD	67	1510.0* m	1340.0-2990.0*	25.17*	22.33-49.83*	0.34
	Propofol	74	1493.0* m	1255.0-2690.0*	24.88*	20.92-44.83*	
Jerath 2015 Discharge readiness time	Isoflurane or Sevoflurane using ACD	67	1662.9 m	1882.7	27.72	31.38	0.18
	Propofol	60	1471.8 m	1763.5	24.53	29.39	
Jabaudon 2017 (SEGA)	Sevoflurane using ACD	25	18.0* d	10.0-37.0*	432.0*	240.0-888.0*	0.9
	Midazolam	25	23.0* d	9.0-43.0*	552.0*	216.0-1032.0*	
Marcos-Vidal 2014	Sevoflurane using ACD	67	44.1 h	30.4	44.1	30.4	0.625
	Propofol	62	46.8 h	31.4	46.8	31.4	
Soro 2012	Sevoflurane using ACD	36	71.0 h	48.0	71.0	48.0	-
	Propofol	37	76.0 h	69.0	76.0	69.0	
Steurer 2012	Sevoflurane using ACD[c]	46	40.1 h	28.8	40.1	28.8	NS
	Propofol[c]	56	40.8 h	38.4	40.8	38.4	
	Sevoflurane using ACD vs. Propofol	102	T/t diff (Unadj): -0.005 d	-0.6-0.6**	-0.12	-14.4-14.4**	NS
		102	T/t diff (Adj[a]): 0.07 d	-0.5-0.7**	1.68	-12.0-16.8**	

ACD: Anaesthetic Conserving Device; Adj: Adjusted; d: Days; h: Hours; IQR: Interquartile range; m: Minute; N: Number of patients; SD: Standard deviation; coloured cells specify calculated data to present results in the same unit of time i.e. hours; T/t diff: treatment difference; Unadj: Unadjusted; [a]The adjusted models included patient age, need for blood products during the case, as well as the duration of extracorporeal circulation and aortic cross-clamp; [b]Data calculated from the subgroup of patients followed up for 6 months (Sackey 2008); [c]Data taken from Spence 2017 meta-analysis sourced from authors

In the **SED001 RCT** mean duration of ICU stay (post-hoc analysis excluding patients switching sedation during 30day follow-up) was lower for isoflurane patients compared to propofol patients (12.67 days vs. 16.9 days, p=0.008). When excluding deaths from this analysis (16 in isoflurane arm, 20 in propofol arm) mean duration of ICU stay was 8.64 days (isoflurane) compared to 14.39 days (propofol), p=0.001.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The well-known pharmacological properties of isoflurane (or sevoflurane) as sedation medicines: rapid on/ offset and minimal metabolism and thus organ toxicity have long been considered to offer greater potential for clinical management flexibility and controllability of mechanically ventilated patients. The AnaConDa device makes inhalational sedation a practicable alternative to standard-of-care IV sedation for mechanically ventilated patients in the ICU. The clinical evidence shows several key benefits:

- There is a strong body of evidence of (at least) non-inferior **sedation efficacy** with regards to time in sedation range and time to extubation and (at least) non-inferior safety and tolerability with regards to all reported adverse events. SED001 RCT has shown this can be achieved with lower **opioid use** and faster time to **spontaneous breathing** for patients.

- SED001 RCT showed isoflurane/AnaConDa to be superior to IV propofol with regards to **wake-up time** after ICU sedation, which aligns with findings from all 8 previous inhalational sedation RCTs identified in the SLR. There is also some evidence that this is associated with faster **cognitive recovery**.

- Differences in **time on a ventilator** associated with sedation regimen has been difficult to show within RCTs in the ICU setting. Six RCTs (SED001 + 5 RCTs in the SLR) all reported less time on a ventilator for inhalational compared to IV sedation, but these were only statistically significant in 2 RCTs in the SLR and in the analysis of SED001 that excluded deaths.

- Differences in **duration of ICU stay** associated with sedation regimen has been difficult to show within RCTs in the ICU setting. All twelve RCTs identified in the SLR showed comparable (non-significant) ICU length of stay.

[redacted]

[redacted]

[redacted]

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The clinical evidence base supports key outcomes as outlined in the decision problem section. There is much good quality evidence (23 RCTs: SED001 + SLR) to support the claimed benefits to the patient: wake-up times, sedation efficacy, cognitive recovery/ psychological outcomes, spontaneous breathing, and opioid use; as well benefits in terms of time on a ventilator and duration of stay in ICU.

More limited evidence is available to support the claim of potential reduction in markers of cardiac, liver, gut, kidney and brain injury. Whilst it is intuitive that inhaled sedation via the lung avoids metabolism through otherwise compromised organs among many ICU patients, empirical evidence of this among the clinical evidence base is harder to identify. The clinical evidence base involves heterogeneity in reasons for ICU admission: SED001 was 40% medical, 56% surgical, 4% trauma and 1% neurosurgical. Ten of the 22 studies in the SLR were specifically for patients post cardiac surgery. Renal integrity was explicitly considered in one study (Rohm 2009). The claim of effective sedation in patients with life-threatening bronchospasm and asthma in supported by the study by Jabaudon et al. 2017.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The clinical evidence base should in general have good external validity to the UK NHS setting. The SED001 RCT was conducted in Germany where ICU clinical practice is likely to be aligned with UK. Within the SLR all except four studies were conducted in Europe. Eighteen studies were conducted in Europe (4 studies each in Germany and Spain, 3 each in the United Kingdom, and Sweden, 2 in France, 1 each in Turkey and Switzerland). Further, two studies

each were conducted in Canada and Egypt. All except one multi-centre study were single centre studies.

Generalisability of the clinical evidence may also be related to the heterogeneity of ICU patients.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

In most invasively ventilated ICU patients, sedation is induced and maintained with intravenous sedatives. These drugs have merit but also drawbacks, especially with increasing doses and prolonged duration. The metabolism and clearance of intravenous sedatives rely on adequate hepatic and renal function. Critically ill patients often have a varying degree of hepatic or renal dysfunction, contributing to a slow elimination of intravenous sedatives and a delayed and unpredictable emergence from sedation.

Inhaled sedation via AnaConDa is eliminated almost exclusively in unchanged form via the airways and is therefore independent of renal or hepatic function. The onset of and recovery from sedation is rapid and predictable.

Clinical studies indicate that the benefits of inhaled sedation via the AnaConDa are more pronounced when isoflurane replaces intravenous sedatives for longer periods. In patients with short-term sedation (<12 hours) a switch to inhaled sedation via the AnaConDa will in most cases only give small additional benefits. For patients with a target of ”no” to light sedation (RASS – 1 to +1), low-dose of intravenous sedatives, may be sufficient and appropriate.

A switch to inhaled sedation via the AnaConDa is therefore appropriate in **patients in need of moderate to deep sedation (RASS -2 to -5) with estimated time of sedation >12 hours**.

Inhaled sedation via the AnaConDa is particularly beneficial in patients with:

- Affected hepatic or renal function
- Patients in which a sedative with a liver and kidney independent elimination would be advantageous

- The opioid sparing effects of inhaled sedation via AnaConDa further strengthen the rationale since opioid elimination also relies on adequate hepatic and renal function.

Bronchospasm

- Patients benefiting from bronchodilatory effects e.g. patients with asthma and COPD

Difficult to sedate

- E.g. patients with high drug tolerance due to alcohol or drug abuse

Deep sedation

- Patients in need of deep and rapid reversible sedation (-4 to -5) e.g. patients undergoing TTM treatment, patients with ARDS, patients in prone positioning

Need of neurological assessments

- Patients where frequent and reliable neurological evaluation is needed e.g. post cardiac arrest patients

Risk of iatrogenic harm from iv sedatives

- Patients with prolonged iv sedation and/or high doses of iv sedatives with risk of accumulation, tolerance development and serious side effects from iv sedation (e.g. delirium, PRIS)

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Strengths of the clinical evidence

- There is a large body of RCT evidence to support the claimed patient and health system benefits.
- SED001 RCT provides robust contemporary evidence in the largest study of its kind.
- Large observational studies support the external validity of the RCT evidence.

Limitations of the clinical evidence

- RCTs tend to be of short duration/ short randomised period.
- Some RCTs in the SLR are smaller sample size.
- Some RCTs in the SLR are old.
- Many RCTs are single centre design.
- RCTs are open label as blinding is impractical/ infeasible.

9 References

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	August 2020
Date span of search:	from database inception to search date
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	

Relevant studies were identified by searching the key biomedical databases suggested by NICE. The key biomedical databases included:

- Embase®
- MEDLINE®
- MEDLINE® In-Process
- Cochrane Central Register of Controlled Trials (CENTRAL)

All databases were searched from inception till 3rd August 2020 to retrieve comprehensive evidence. Search strategies for MEDLINE® and Embase® were implemented using the Embase.com platform, MEDLINE® In-Process using the PubMed platform, and CENTRAL using the Wiley Online platform.

Table 13: Search strategy for Embase® and MEDLINE® using Embase.com

S. No	Query	Hits
1	'conscious sedation'/exp	7,627
2	'artificial ventilation'/exp	205,203
3	'artificial respiration' OR 'controlled respiration' OR 'controlled ventilation' OR 'mechanical respiration' OR 'mechanical ventilation' OR ventilat* OR 'anesthesia conserving device' OR 'anaesthesia conserving device'	329,414
4	'intensive care'/exp OR icu:ab,ti	766,762
5	(mechanical* OR artificial*) NEAR/5 ventilat*	162,103
6	'critical illness' OR 'critical care'	384,188
7	#2 OR #3 OR #4 OR #5 OR #6	1,038,360
8	sedation:ab,ti OR sedat*:ab,ti	87,989
9	#1 OR (#7 AND #8)	28,345
10	'desflurane'/exp OR 'desflurane'/syn OR 'i 653':ab,ti OR sulorane:ab,ti OR suprane:ab,ti	5,894
11	'isoflurane'/exp OR 'isoflurane'/syn OR forane:ab,ti OR forene:ab,ti OR forthane:ab,ti OR isoflurano:ab,ti OR isorane:ab,ti OR sofloran:ab,ti	28,160
12	'sevoflurane'/exp OR 'sevoflurane'/syn OR sevocalm:ab,ti OR sevoflo:ab,ti OR sevofrane:ab,ti OR sevohale:ab,ti OR sevorane:ab,ti OR sevotec:ab,ti OR sojourn:ab,ti OR ultane:ab,ti	22,276
13	'dexmedetomidine'/exp OR 'dexmedetomidine'/syn OR cepedex:ab,ti OR dexamedetomidine:ab,ti OR dexdomitor:ab,ti OR dexdor:ab,ti OR 'dexmedetomidine hydrochloride':ab,ti OR 'mpv 1440':ab,ti OR 'mpv1440':ab,ti OR precedex:ab,ti OR primadex:ab,ti OR sedadex:ab,ti OR sileo:ab,ti	11,549
14	'clonidine'/exp OR 'clonidine'/syn OR clonidine:ab,ti OR clofenil:ab,ti OR klofenil:ab,ti OR m5041t:ab,ti OR 'm 5041t':ab,ti OR catapres*:ab,ti OR 'st155':ab,ti OR 'st 155':ab,ti	43,963
15	'propofol'/exp OR 'propofol'/syn OR cryotol:ab,ti OR diisoprofol:ab,ti OR diprivan:ab,ti OR diprofol:ab,ti OR disoprivan:ab,ti OR disoprofol:ab,ti OR fresofol:ab,ti OR gobbifol:ab,ti OR 'ici 35 868':ab,ti OR 'ici 35868':ab,ti OR plofed:ab,ti OR pofol:ab,ti OR profast:ab,ti OR propocam:ab,ti OR 'propofol lipuro':ab,ti OR 'propofol-lipuro':ab,ti OR 'propolipid':ab,ti OR 'propoven':ab,ti OR 'provive':ab,ti OR apinovet:ab,ti OR rapiva:ab,ti OR recofol:ab,ti OR 'recofol n':ab,ti	55,751
16	'midazolam'/exp OR 'midazolam'/syn OR midacum:ab,ti OR midafresa:ab,ti OR midazo:ab,ti OR midazol:ab,ti OR 'midazolam hydrochloride':ab,ti OR midolam:ab,ti OR miloz:ab,ti OR nayzilam:ab,ti OR 'nvd 301':ab,ti OR 'nvd301':ab,ti OR 'ro 21 3981':ab,ti OR 'ro 21-3981':ab,ti OR 'ro 21-3981-003':ab,ti OR 'ro 213981':ab,ti OR 'ro 213981003':ab,ti OR 'ro21 3981':ab,ti OR 'ro21 3981 003':ab,ti OR 'ro21-3981':ab,ti OR 'ro21-3981-003':ab,ti	50,220

	OR 'ro213981':ab,ti OR 'ro213981003':ab,ti OR 'seizalam':ab,ti OR 'shp 615':ab,ti OR 'shp615':ab,ti OR 'suda 003':ab,ti OR 'suda003':ab,ti OR 'usl 261':ab,ti OR 'usl261':ab,ti OR versed:ab,ti	
17	'lorazepam'/exp OR 'lorazepam'/syn OR almazine:ab,ti OR alzapam:ab,ti OR anxiedin:ab,ti OR anxira:ab,ti OR anzepam:ab,ti OR aplacasse:ab,ti OR 'apo lorazepam':ab,ti OR aripax:ab,ti OR ativan:ab,ti OR azurogen:ab,ti OR bonatranquan:ab,ti OR duralozam:ab,ti OR efasedan:ab,ti OR emotival:ab,ti OR kalmalin:ab,ti OR kendol:ab,ti OR larpose:ab,ti OR laubeel:ab,ti OR lonza:ab,ti OR lopam:ab,ti OR lorabenz:ab,ti OR loram:ab,ti OR loranase:ab,ti OR loranaze:ab,ti OR lorans:ab,ti OR lorapam:ab,ti OR loravan:ab,ti OR lorax:ab,ti OR loraz:ab,ti OR lorazene:ab,ti OR lorazep:ab,ti OR 'lorazepam intensol':ab,ti OR lorazin:ab,ti OR lorazon:ab,ti OR lorenin:ab,ti OR loridem:ab,ti OR lorivan:ab,ti OR lorsedal:ab,ti OR lorzem:ab,ti OR merlit:ab,ti OR mesmerin:ab,ti OR 'nervistop l':ab,ti OR novhepar:ab,ti OR 'novo lorazem':ab,ti OR orfidal:ab,ti OR orifadal:ab,ti OR placinoral:ab,ti OR 'pro dorm':ab,ti OR punktyl:ab,ti OR quait:ab,ti OR renaquil:ab,ti OR rocosgen:ab,ti OR securit:ab,ti OR sinestron:ab,ti OR stapam:ab,ti OR tavor:ab,ti OR temesta:ab,ti OR titus:ab,ti OR tranqipam:ab,ti OR trapax:ab,ti OR trapex:ab,ti OR 'wy 4036':ab,ti	33,549
18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	195,150
19	('clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR (allocated NEAR/2 random) OR (random* NEAR/1 assign*) OR random* OR ((single OR double OR triple OR treble) NEAR/1 (blind* OR mask*))) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	9,843,356
20	'time to emergence' OR 'time to extubation'	1,221
21	#9 AND #18 AND (#19 OR #20)	5,765
22	#21 AND ([conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR [review]/lim)	542
23	#21 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	294
24	#21 AND (paediatric:ti OR pediatric:ti OR child*:ti OR infant*:ti OR neonat*:ti) NOT adult*:ti	797
25	#22 OR #23 OR #24	1,544
26	#21 NOT #25	4,221
27	#26 AND [conference abstract]/lim	993
28	#26 NOT #27 (removing conference abstracts)	3,228

Searched on 3rd August 2020

Table 14: Search strategy for MEDLINE® In-Process searched via PubMed® platform

S. No	Query	Hits
1	"conscious sedation"[MeSH Terms]	8,849
2	"conscious sedation"	10,365
3	artificial ventilation[MeSH Terms]	76,334
4	"artificial ventilation" OR "artificial respiration" OR "controlled respiration" OR "controlled ventilation" OR "mechanical respiration" OR "mechanical ventilation"	77,242
5	"intensive care"	2,50,527
6	intensive care[MeSH Terms]	57,356
7	icu[Title/Abstract]	55,564
8	(mechanical* OR artificial*) AND ventilat*	79,779

9	"critical illness" OR "critical care"	2,02,046
10	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	4,71,677
11	sedation OR sedat*	78,444
12	#10 AND #11	12,280
13	#1 OR #2	10,365
14	#12 OR #13	20,535
15	desflurane OR "i 653" OR sulorane OR suprane	2,396
16	isoflurane OR forane OR forene OR forthane OR isoflurano OR isorane OR sofloran	14,412
17	sevoflurane OR sevocalm OR sevoflo OR sevofrane OR sevohale OR sevorane OR sevotec OR sojourn OR ultane	10,484
18	dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR "dexmedetomidine hydrochloride" OR "mpv 1440" OR "mpv1440" OR precedex OR primadex OR sedadex OR sileo	6,203
19	clonidine OR clofenil OR klofenil OR m5041t OR "m 5041t" OR catapres* OR "st155" OR "st 155"	18,392
20	propofol OR cryotol OR diisoprofol OR diprivan OR diprofol OR disoprivan OR disoprofol OR fresofol OR gobbifol OR "ici 35 868" OR "ici 35868" OR plofed OR pofol OR profast OR propocam OR "propofol lipuro" OR propofol-lipuro OR propolipid OR propoven OR provive OR apinovet OR rapiva OR recofol OR "recofol n"	22,414
21	midazolam OR midacum OR midafresa OR midazo OR midazol OR "midazolam hydrochloride" OR midolam OR miloz OR nayzilam OR nvd301	14,492
22	lorazepam OR almazine OR anxiedin OR anxira OR anzepam OR aplacasse OR "apo lorazepam" OR aripax OR ativan OR azurogen OR bonatranquan OR duralozam OR efasedan OR emotival OR kalmalin OR larpose OR laubeel OR lonza OR lopam OR lorabenz OR loram OR lorans OR lorapam OR lorax OR loraz OR lorazene OR lorazep OR "lorazepam intensol" OR lorazin OR lorazon OR lorenin OR loridem OR lorivan OR lorsedal OR lorzem OR merlit OR "nervistop l" OR novhepar OR orfidal OR "pro dorm" OR punktyl OR quait OR renaquil OR rocosgen OR securit OR sinestron OR stapam OR temesta OR tranqipam OR trapax OR trapex	5,411
23	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	79,017
24	#14 AND #23	7,176
25	#24 AND (inprocess[sb] OR pubstatusaheadofprint)	209

Searched on 3rd August 2020

Table 15: Search strategy for CENTRAL searched via Cochrane library

S. No	Query	Hits
1	MeSH descriptor: [Conscious Sedation] explode all trees	1,389
2	"conscious sedation"	2,269
3	MeSH descriptor: [Respiration, Artificial] explode all trees	6,053
4	"artificial ventilation" OR "artificial respiration" OR "controlled respiration" OR "controlled ventilation" OR "mechanical respiration" OR "mechanical ventilation" OR “ventilat*” OR anaconda OR “anesthesia conserving device” OR “anaesthesia conserving device”	12,171
5	"intensive care"	30,851
6	MeSH descriptor: [Critical Care] explode all trees	2,020
7	(icu):ti	1,636
8	(mechanical* OR artificial*) AND ventilat*	14,886
9	"critical illness" OR "critical care"	21,522
10	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	54,516

11	sedation OR sedat*	24,188
12	#10 AND #11	3,796
13	#1 OR #2	2,269
14	#12 OR #13	5,721
15	desflurane OR "i 653" OR sulorane OR suprane	1,626
16	isoflurane OR forane OR forene OR forthane OR isoflurano OR isorane OR sofloran	4,044
17	sevoflurane OR sevocalm OR sevoflo OR sevofrane OR sevohale OR sevorane OR sevotec OR sojourn OR ultane	5,775
18	dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR "dexmedetomidine hydrochloride" OR "mpv 1440" OR "mpv1440" OR precedex OR primadex OR sedadex OR sileo	4,779
19	clonidine OR clofenil OR klofenil OR m5041t OR "m 5041t" OR catapres* OR "st155" OR "st 155"	4,124
20	propofol OR cryotol OR diisoprofol OR diprivan OR diprofol OR disoprivan OR disoprofol OR fresofol OR gobbifol OR "ici 35 868" OR "ici 35868" OR plofed OR pofol OR profast OR propocam OR "propofol lipuro" OR propofol-lipuro OR propolipid OR propoven OR provive OR apinovet OR rapiva OR recofol OR "recofol n"	13,757
21	midazolam OR midacum OR midafresa OR midazo OR midazol OR "midazolam hydrochloride" OR midolam OR miloz OR nayzilam OR nvd301	8,593
22	lorazepam OR almazine OR anxiedin OR anxira OR anzepam OR aplacasse OR "apo lorazepam" OR aripax OR ativan OR azurogen OR bonatranquan OR duralozam OR efasedan OR emotival OR kalmalin OR larpose OR laubeel OR lonza OR lopam OR lorabenz OR loram OR lorans OR lorapam OR lorax OR loraz OR lorazene OR lorazep OR "lorazepam intensol" OR lorazin OR lorazon OR lorenin OR loridem OR lorivan OR lorsedal OR lorzem OR merlit OR "nervistop l" OR novhepar OR orfidal OR "pro dorm" OR punktyl OR quait OR renaquil OR rocosgen OR securit OR sinestron OR stapam OR temesta OR tranqipam OR trapax OR trapex	2,132
23	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	32,504
24	#14 AND #23	3,181
25	#24 in Trials	3,060
26	#25 NOT (pubmed OR embase):an	606
27	#26 NOT (paediatric OR pediatric OR child* OR infant*):ti	543
28	#27 NOT (ctgov OR ictrp):an	109

Searched on 3rd August 2020

Table 16: Combined hits from all databases

S. No	Database	Hits
1	Embase® and MEDLINE®	3,228
2	MEDLINE® In-Process	209
3	CENTRAL	109
4	Total	3,546

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Conference abstracts were hand searched for the last three years to retrieve the latest clinical studies, which have not yet been published in journals as full-text articles. The relevant conferences for abstract screening include:

- o European Society of Intensive Care Medicine (ESICM): 2018-2020
- o Society of Critical Care Medicine (SCCM): 2018-2020

Inclusion and exclusion criteria:

The PICOS elements were used to guide the identification and selection of studies that are relevant for the evidence synthesis

Table 17: PICOS eligibility criteria for broader objective

PICOS	Inclusion Criteria		
Participants	o Mechanically ventilated adult patients (>18 years) requiring sedation		
Interventions	o Isoflurane o Sevoflurane o Desflurane	o Propofol o Dexmedetomidine o Clonidine	o Midazolam o Lorazepam
Comparators	o Placebo o Any included intervention	o Haloperidol o Morphine	
Study Design	o Randomised controlled trials (RCTs) irrespective of blinding status		
Language	o No restriction on language		
Publication timeframe	o Database inception to present		

Table 18: PICOS eligibility criteria for the specific objective (inhalational versus intravenous sedatives)

PICOS	Inclusion Criteria	
Participants	o Mechanically ventilated adult patients (>18 years) requiring sedation	
Interventions	o Isoflurane o Sevoflurane o Desflurane	
Comparators	o Placebo o Any included intervention o Propofol o Dexmedetomidine o Clonidine	o Midazolam o Lorazepam o Haloperidol o Morphine
Study Design	o RCTs irrespective of blinding status	

Language	○ No restriction on language
Publication timeframe	○ Database inception to present

Data abstraction strategy:

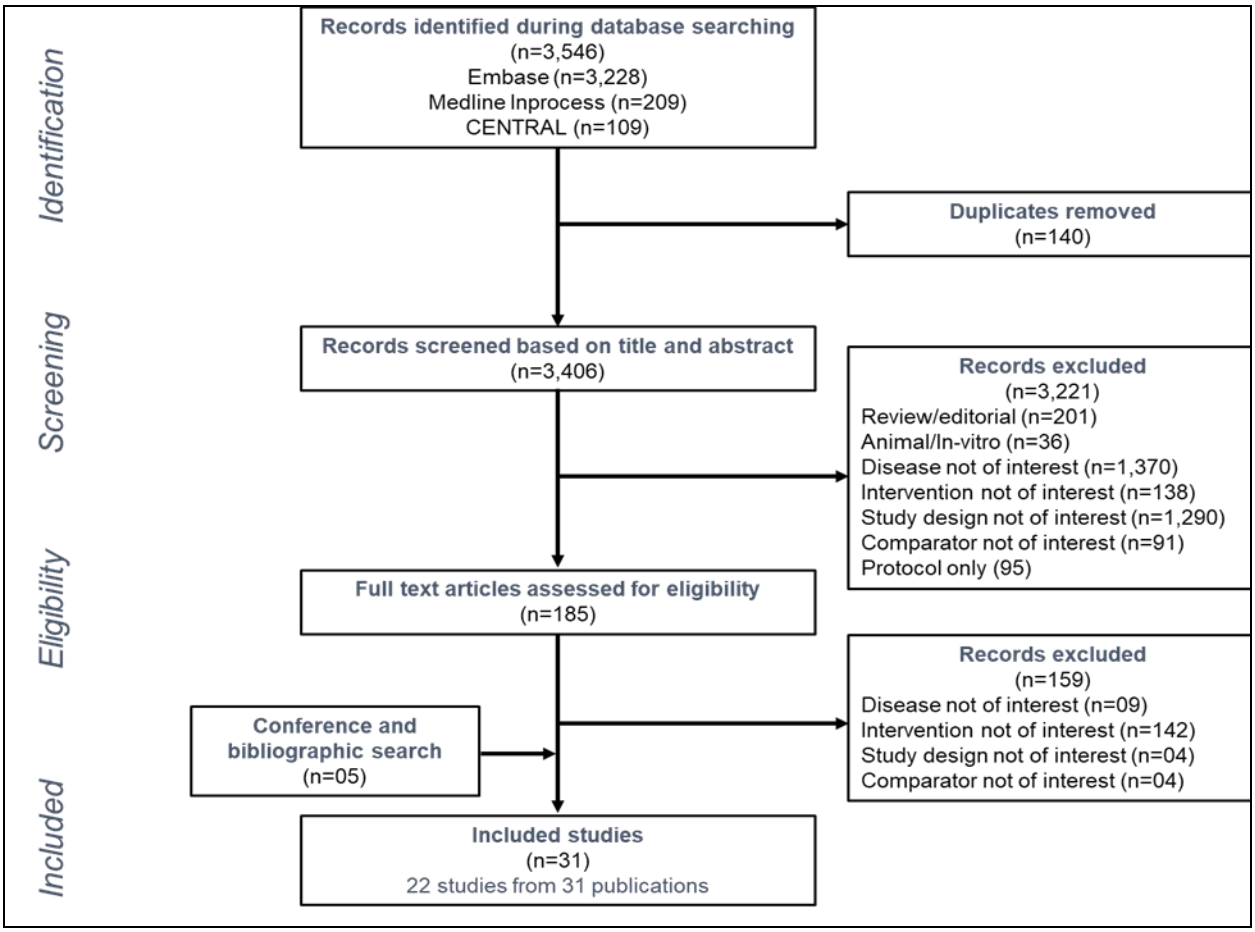
Two investigators working independently extracted data on study characteristics, interventions, patient characteristics, and outcomes for the study population of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors were resolved by discussion and coming to a consensus. Data were entered into a Microsoft Excel Workbook.

Excluded studies

A list of excluded studies is provided as an embedded XLS file below. These are studies that were initially considered for inclusion at the level of full text review but were later excluded for specific reasons. As detailed in the PRISMA flow below, a total of 159 publications were excluded primarily due to the intervention not of interest (n=142).

Clinical SLR in MV sedation_List of exclu

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Risk of Bias

The critical appraisal of included studies was conducted using comprehensive assessment criteria based on the recommendations in the NICE manufacturer's template. Table 19 presents the risk of bias assessment of the included RCTs based on a NICE checklist. All 22 studies were randomised trials. The method of randomisation was adequate in 14 trials, and it was inadequate in two trials (Guerrero 2013, Marcos-Vidal 2014). However, this information was not reported in six trials. Similarly, the method of allocation concealment was adequate in 13 trials, not reported in seven trials and inadequate in two trials. Most of the included studies were associated with a high risk of bias due to open-label or single-blind nature. Only two studies used an adequate double-blind setting for conducting the trials (Soro 2012, Kong 1989). Other studies mainly cited the logistic issues to conduct the double-blind trial due to the complex nature of the disease area and patient care requirements.

Most of the studies exhibited a low risk of bias in terms of all other critical appraisal parameters including variability in baseline characteristics, study withdrawals, outcome selection, and reporting, and statistical analysis.

Table 19: Quality assessment among the included RCTs

Study name	Random sequence generation	Allocation concealment	Baseline parameters	Blinding of participants and personnel	Blinding of outcome assessment	Withdrawals	Selective reporting	Type of analysis
Sackey 2007	?	?	+	-	+	+	+	+
Hanafy 2005	+	+	+	-	-	+	+	+
Sackey 2004	?	?	+	-	-	+	+	+
Spencer 1992	?	?	+	?	?	?	+	-
Kong 1989	?	?	+	+	+	?	+	-
Walczak 2019 VALTS sub study	+	+	+	-	-	?	-	-
Jerath 2015	+	+	+	-	+	+	+	+
Gomez 1995	+	?	+	?	?	+	+	+
Millane 1992	?	?	+	?	?	+	+	+
Jabaudon 2017 (SEGA)	+	+	+	-	-	+	+	+
Marcos-Vidal 2014	-	-	+	-	-	+	+	-
Guerrero 2013	-	-	+	-	-	+	+	+
Soro 2012	+	+	+	+	+	+	+	+
Steurer 2012	+	+	+	-	-	+	+	+
Hellstrom 2012	+	+	+	-	-	+	+	+
Mesnil 2011	+	+	+	-	-	+	+	+
Rohm 2009	+	+	+	-	+	+	+	+
Rohm 2008	+	+	+	-	+	+	+	+
Turktan 2019	+	+	+	?	?	+	+	+
Meiser 2003	+	+	-	-	-	+	+	-
Bellgardt 2019	+	+	+	+	-	+	+	+
El 2016	?	?	?	?	?	?	?	?

+ Low risk - High risk ? Unclear

In the SLR update (439 hits), checking for the duplicates resulted in the exclusion of 61 hits, and the remaining 378 hits were screened. After preliminary screening of title/abstracts, 363 records were excluded, and 15 records were included for full publication screening. After a secondary screening of full-text articles, 13 studies were excluded. Additionally, one study (Eudra CT#: 2016-004551-67) was included from the conference searching. Ultimately, this resulted in the inclusion of three publications assessing at least one group of inhalational sedatives in the clinical update SLR. Figure 4 presents the PRISMA flow diagram of studies identified during the SLR update.

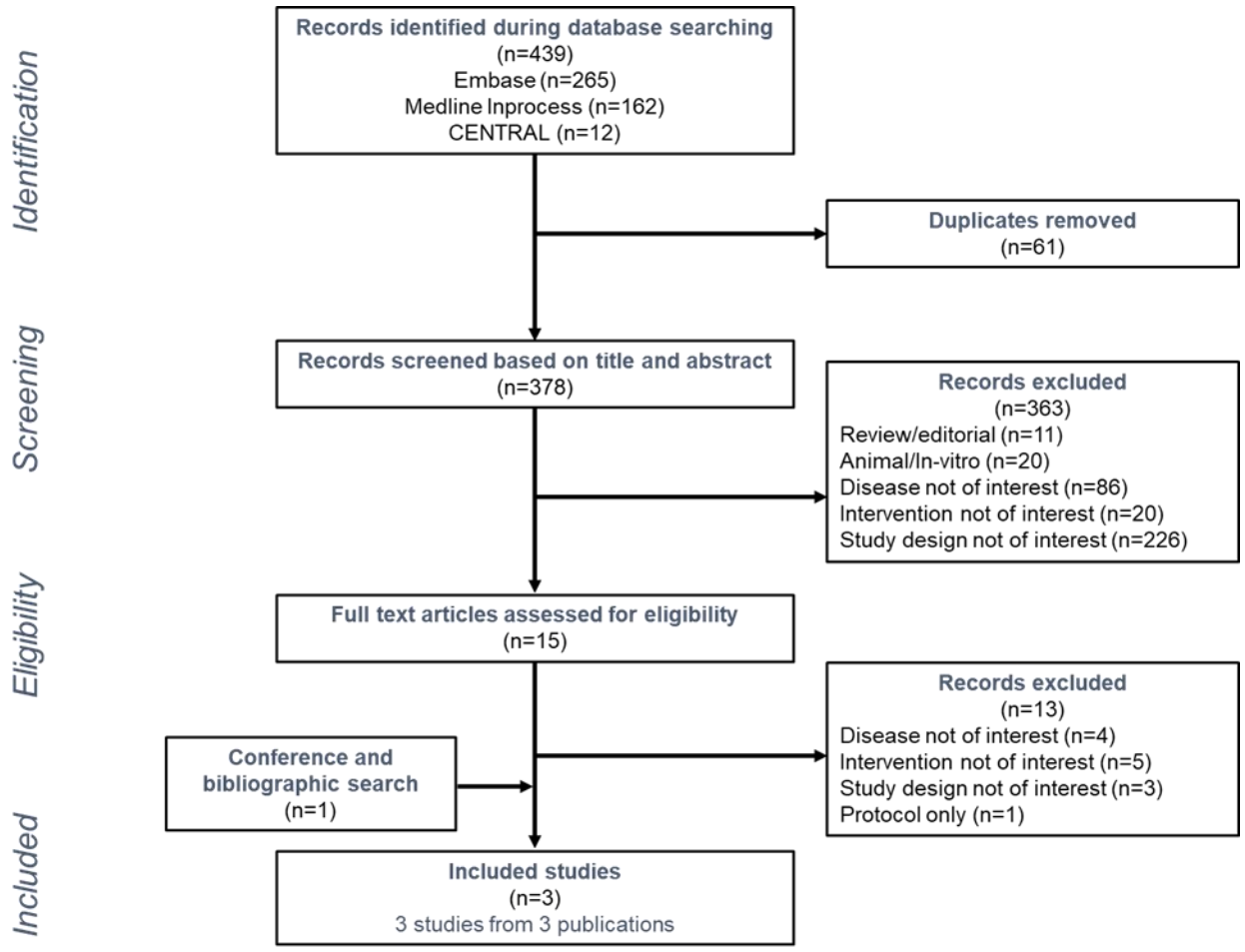


Figure 4: PRISMA for SLR update (14th April 2021)

[redacted]

[redacted]

Appendix B: Search strategy for adverse events

Adverse events were included as an outcome in the SLR. The search strategy is details in Appendix A above.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
23	☐ Commercial in confidence ☒ Academic in confidence	SED001 has not been fully published at this time. (First report was given at ESICM congress in Dec 2020 (Meiser et al. 2020)). Until full details are publicly available SED001 results are provided here as academic in confidence.	Full publication expected in 2021.
Details	Table 6 – report of SED001 study results.		
29	☐ Commercial in confidence ☒ Academic in confidence	SED001 has not been fully published at this time. (First report was given at ESICM congress in Dec 2020 (Meiser et al. 2020)). Until full details are publicly available SED001 results are provided here as academic in confidence.	Full publication expected in 2021.
Details	Section 5 – report of SED001 study results		

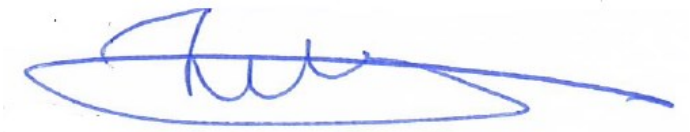
44	☐ Commercial in confidence ☒ Academic in confidence	SED001 has not been fully published at this time. (First report was given at ESICM congress in Dec 2020 (Meiser et al. 2020)). Until full details are publicly available SED001 results are provided here as academic in confidence.	Full publication expected in 2021.
Details	Adverse events – report of SED001 study results		
56-57	☐ Commercial in confidence ☒ Academic in confidence	SED001 has not been fully published at this time. (First report was given at ESICM congress in Dec 2020 (Meiser et al. 2020)). Until full details are publicly available SED001 results are provided here as academic in confidence.	Full publication expected in 2021.
Details	Figure 3 – report of SED001 study results		
66	☐ Commercial in confidence ☒ Academic in confidence	SLR/ meta-analysis is unpublished at this time	Full publication expected in 2021.
Details	Appendix A – SLR results		
79	☐ Commercial in confidence ☒ Academic in confidence	SED001 has not been fully published at this time. (First report was given at ESICM congress in Dec 2020 (Meiser et al. 2020)). Until full details are publicly available SED001 results are provided here as academic in confidence.	Full publication expected in 2021.
Details	Structured abstract (unpublished) – report of SED001 study results		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	April 27, 2021
Print:	Jens Lindberg	**Role / organisation:**	VP Commercial Operations
Contact email:	jens.lindberg@sedanamedical.com		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT582 AnaConDa-S for sedation with volatile anaesthetics in intensive care

Company evidence submission

Part 2: Economic evidence

Company name	Sedana Medical
Submission date	25th May 2021
Contains confidential information	Yes

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1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		571
Number of studies identified as being relevant to the decision problem.		2
Of the relevant studies identified:	Number of published studies.	1
	Number of abstracts.	1
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Conference abstract	Sackey et al. 2018; German clinical data	Clinical data were taken from a German observational study (Bellgardt et al 2016) in long-term ventilated, surgical patients.	Intervention: isoflurane (using AnaConDa). Comparator: propofol/midazolam	Sedation cost per day: intervention (drug and device) £97.38; comparator (drug only) £20.96	Outcomes: in-hospital mortality and 365-day mortality. Results: Over 5 years an estimated 31 in-hospital deaths and 25 deaths at 365 days could be avoided per 100 patients sedated with isoflurane versus propofol/midazolam.	Over five years, the usage of the AnaConDa technology could significantly reduce mortality. These reductions in mortality are associated with an incremental cost per patient of £1,677. The total cost per death avoided is £7,943.
Journal article	L'Her et al. 2008; French clinical data	This study included 15 patients who required > 24 hours of deep sedation receiving firstly conventional intravenous sedation (benzodiazepine and opioid) according to a sedation protocol and then switched to inhaled isoflurane via the AnaConDa.	Intervention: Isoflurane using AnaConDa. Comparator: midazolam	Intervention: €119±38 for the first 24 hours of isoflurane sedation. €122±44 as the mean isoflurane sedation cost in all patients. €110±19 as the mean isoflurane sedation cost among the 7 patients who had an above average midazolam requirement (0.4 mg/kg/h). Comparator: €171±101 for conventional sedation (24-Hour period before initiating Isoflurane). €218±111 among the 7 patients who had an above average midazolam requirement (0.4mg/kg/h).	The overall daily cost of the 2 sedation protocols was not different in the whole group of 15 patients, but in the subgroup of 7 patients who required a mean midazolam infusion larger than the average dose, the cost difference was very significant (€218±111 vs €110±19, P < .01)	Isoflurane significantly decreases sedation cost in some patients. In our ICU we now use isoflurane as a standard sedation tool in certain cases, especially when deep sedation is required during the initial phase of care.

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Sackey et al. 2018	
What are main differences in resource use and clinical outcomes between the technologies?	Over 5 years an estimated 31 in-hospital deaths and 25 deaths at 365 days could be avoided per 100 patients sedated with isoflurane versus propofol/midazolam. These reductions in mortality are associated with an incremental cost per patient of £1,677.
How are the findings relevant to the decision problem?	Population, intervention, and comparators are relevant to the decision problem. The outcome in terms of comparative costs is relevant to the decision problem, however, the outcome of mortality is not explicitly included in decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	The overall cost per death avoided is estimated to be £7,943.
What are the limitations of this evidence?	The clinical data is based on a German observational study to inform a UK decision analytic model. Bellgardt 2016 study was performed in a small group of adult patients ventilated for over 96 hours. Therefore, the results may not be directly generalisable to all ICU patient populations.
How was the study funded?	The study was funded by Sedana Medical and presented as an ISPOR congress poster
L'Her et al. 2008	
What are main differences in resource use and clinical outcomes between the technologies?	Sedation efficacy (Ramsey score) was similarly achieved with both strategies. Isoflurane sedation via the AnaConDa lowers sedation cost in patients who require prolonged sedation and patients in whom it is difficult to reach the sedation goal with standard sedation doses.

How are the findings relevant to the decision problem?	PICO relevance
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, supportive of cost benefits versus IV midazolam.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	The overall daily cost of the 2 sedation protocols was not different in the whole group of 15 patients, but in the subgroup of 7 patients who required a mean midazolam infusion larger than the average dose, the cost difference was very significant (€218±111 vs €110±19, P < .01).
What are the limitations of this evidence?	Open pragmatic study design. Cross-over design may have some carry over effects.
How was the study funded?	Institutional funding only

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

The patients are mechanically ventilated adult patients (>18 years) requiring sedation for ≥24 hours in the ICU.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The intervention technology is isoflurane (a volatile inhaled anaesthetic) and is administered via the Anaesthetic Conserving Device (AnaConDa) delivery system. Standard-of-care IV sedation is primarily propofol or midazolam (dexmedetomidine is licensed but less widely used in this context). The choice of propofol or midazolam may depend on the clinical context and expected duration of sedation needed. Longer-term use of propofol may be avoided due to accumulation and tolerance issues whereas the use of midazolam may bring issues known to be associated with benzodiazepines. In some patients both IV strategies maybe used sequentially. In order to be most informative to payer/HTA decision-makers the base-case model provides two separate comparisons: • isoflurane (via AnaConDa) vs. IV Propofol • isoflurane (via AnaConDa) vs. IV Midazolam

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The rationale for a cost-consequence analysis was based on the decision problem; alignment with the economic studies identified in the literature searches; and the universal value of the economic information to decision-makers in all payer archetypes as this methodology also provides a cost-benefit analysis by estimating overall net-monetary impact at a patient and population-level.

Since there is no clinical evidence supporting a difference in efficacy between sedation treatments, a cost-effectiveness analysis or a cost-utility analysis would not be appropriate. Moreover, although control of sedation facilitating flexible clinical management has a positive impact on patient quality of life, these effects occur only for relatively short periods of time. Consequently, estimation of quality-adjusted life-years (QALYs) resulting from this intervention would be inadequate. The dexmedetomidine submission to SMC (SMC, 2012) was a base-case presented as a cost-minimisation analysis, and a supplementary analysis attempting a cost-utility analysis. In the latter case the submitting company valued QALYs at £25k and used a net benefit analysis approach to avoid the instability in an incremental cost effectiveness ratio (ICER) produced by a very small denominator (given the short time horizon). Based on arbitrary assignment of utility values (ICU intubation 0.1, hospital stay 0.5) dexmedetomidine was estimated to provide 0.001 QALYs over a 45day period. The base-case cost-minimisation analysis was considered more informative.

The model structure in this submission is based on a decision-analytic model with the key data inputs of sedation costs (drug acquisition costs, dose intensity, costs of administration & monitoring) and ICU costs (unit costs, time in ICU, mechanical ventilation time). Additionally, data can be added for estimates of the eligible population and the market share uptake rate in order to present budget impact analysis over a five-year period.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Sedation efficacy, tolerability and safety are **not** different by sedation strategy (isoflurane via AnaConDa vs. IV SoC sedation)	SED001 demonstrated non-inferiority. Clinical SLR found no evidence to support differences in these metrics.	SED001 RCT, clinical SLR (part 1 submission)
Sedation costs, monitoring and administration do differ by sedation strategy (isoflurane via AnaConDa vs. IV SoC sedation)	Although there are only small differences in sedation drug costs device/ equipment/ consumables costs are clearly different by sedation strategy. Dose renewal (drug administration) will be much more frequent with IV sedation than inhaled isoflurane. Daily sedation interruption protocols are much more likely with IV sedation in order to avoid accumulation.	UK Clinical KoL validation

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Duration of mechanical ventilation #1	[redacted]	[redacted]	[redacted]	[redacted]
Duration of mechanical ventilation #2	Observational study: Krannich et al. 2017, N=220	Delta = 4.1 days, **p=0.003** (Isoflurane median 7.1 days, Midazolam median 11.2 days)	IQR Isoflurane (87-323hrs) Midazolam (122-530hrs)	Scenario analysis (vs midazolam) based on 4.1 days delta.
Duration of mechanical ventilation #3	[redacted]	[redacted]	[redacted]	[redacted]
ICU duration #1	[redacted]	[redacted]	[redacted]	[redacted]
ICU duration #2	Observational study: Krannich et al. 2017, N=220	Delta 5 days, **p=0.006** (Isoflurane median 8 days,	IQR Isoflurane (4-16 days)	Scenario analysis (vs midazolam) based on 5 days delta.

		Midazolam median 13 days	Midazolam (6-27 days)	
ICU duration #3	RCT SED001 30day follow-up (including switchers), [redacted]	Delta [redacted] (Isoflurane mean [redacted] days, Propofol mean [redacted] days)	SD (MV-free days) Isoflurane [redacted] Propofol [redacted]	Scenario analysis (vs propofol) based on [redacted] days delta.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

N/A

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification
Time horizon	ICU episode (up to 30 days post randomisation)	As per NICE guidance
Discount rate	N/A	
Perspective (NHS/PSS)	NHS	
Sources of unit costs	NHS Reference costs, BNF, Company price list	

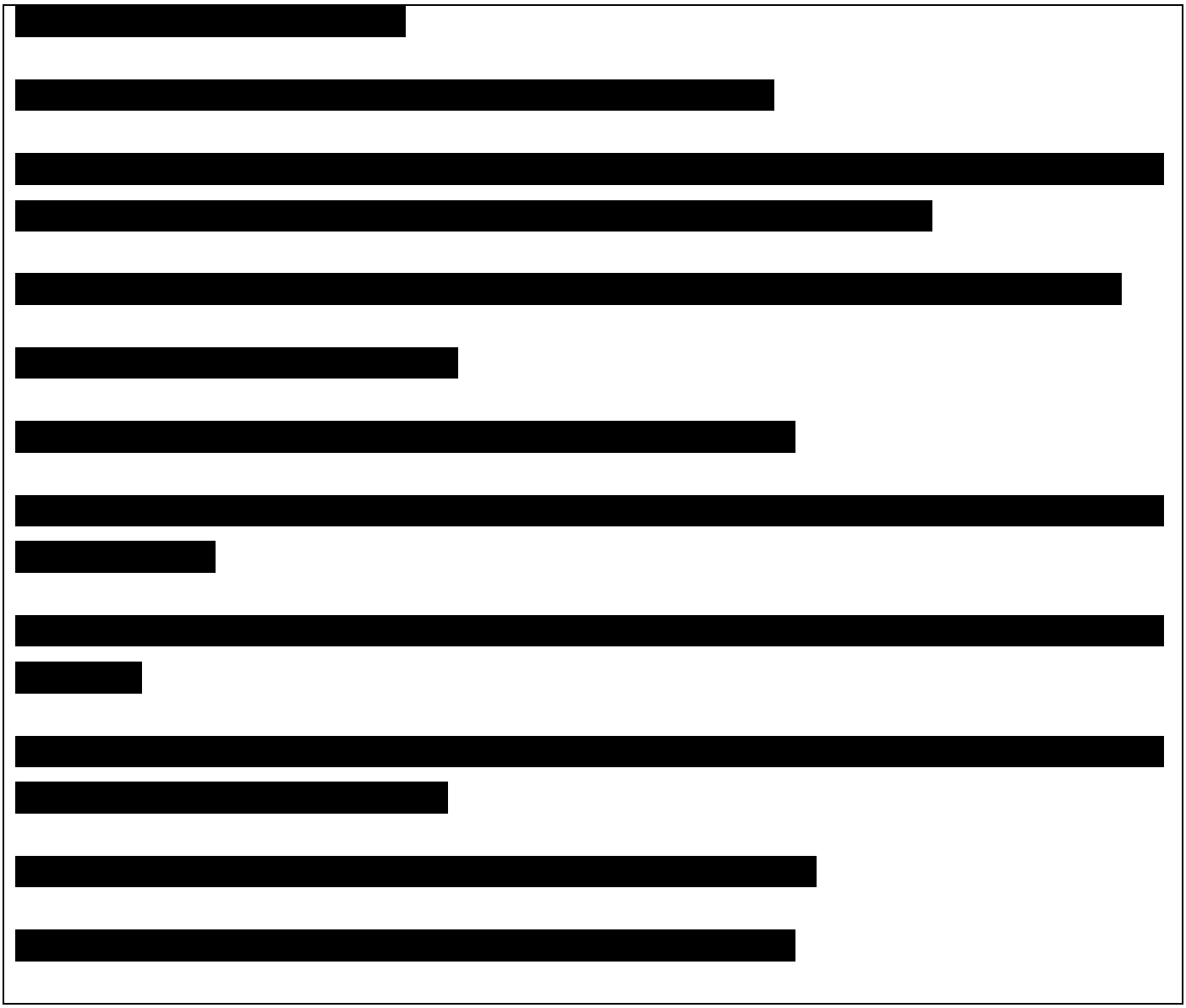
Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

N/A

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).



[redacted]

If the list price is not used in the model, provide the price used and a justification for the difference.

N/A

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

For ICU costs the model uses the NHS Reference costs. For an ICU bed day with mechanical ventilation a unit cost of £1,218 is used (NHS Reference Costs. Main Schedule. 2018/19. National average unit cost for critical care). For a non-ventilated ICU bed day a unit cost of £933 is used (NHS Reference Costs. Main Schedule. 2018/9. CCU01 Non-specific, general adult critical care patients predominate. Adult Critical Care, 0 Organs Supported). These costs are conservative.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

See Appendix A

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Resources needed have been clearly identified and costed in the NICE MIB229. Except for the procurement of the AnaConDa and associated consumables, ventilation, syringe pumps and staffing, resources should remain unchanged.

Standard syringe driver pumps are needed but these are standard ICU equipment.

Gas monitoring: some units will already have this ability, but others will need to adapt their current monitors by buying a gas module or purchase a stand-alone monitor.

The ability to scavenge from the ventilator on the exhaust port: most ventilators have an exhaust port (except for the oxylog transport vent) so there are no additional resources in regard to scavenging.

All other equipment needed is supplied in the AnaConDa starter kit.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources are required. Nurses will continue to use RASS for assessment of sedation depth. Gas monitor will provide the MAC.

In terms of nursing time there should be a reduction in time needed to manage patient's sedation compared to IV sedation. Single drug sedation as opposed to poly-pharma often required.

Reduction in consumables such as syringes or giving sets for propofol.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

No additional resources are required.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

		Technology (isoflurane via AnaConDa) costs	Comparator (Propofol) costs	Difference in resource use costs
Sedation costs	Duration of sedation	[redacted] Base case is mean duration based on RCT SED001 (non-switchers) across both arms		0
	Drug costs (per sedated patient)	£111 Isoflurane 3ml per hour	£228 Propofol 3mg/kg/hour (70kg patient)	-£117
	Non-drug costs (per sedated patient)	[redacted] AnaConDa Syringes New fill adapter FlurAbsorb Measure line Nafion tubing Gas analyser Accessories kit	£546 Dose renewal time & consumables (10 per day) Daily sedation interruption protocol	[redacted]
	Sub-total	£1,044	£774	£270
ICU costs	Duration of ICU Base case is mean duration based on RCT SED001 (non-switchers)	[redacted]	[redacted]	[redacted]
	Sub-total (MV days @ £1,218 Non-MV days @ £933)	£14,956	£18,874	-£3,919
Total costs	**Per sedated patient**	**£16,090**	**£19,648**	**-£3,649**

Duration of sedation can be varied in the model, the base case uses data from the SED001 study. Sedation dose intensity for the intravenous drugs can be varied in the model, the base case uses the midpoint of prescribed guidance ranges (propofol: 1.5-4.5 mg/kg/hour). As this dosing is

weight-based, mean patient weight can be varied in the model. Sedation dose intensity for isoflurane can be varied in the model, the base case is 3ml/hour.

Unit costs for IV drug acquisition are taken from publicly available UK NHS sources (Drugs and pharmaceutical electronic market information tool (eMIT) - GOV.UK (www.gov.uk)). The eMIT provides information about prices and usage for generic drugs and pharmaceutical products with the average price paid for a product over the last 4 months of the period. The data within the eMIT represents the 12-month period to the end of December 2019.

Normal ICU patient monitoring is assumed to be the same for IV sedation or AnaConDa patients, however, two key inherent differences are apparent. First, IV sedation requires more frequent dose renewal that involves access to secure drugs store and cross-check verification with multiple colleagues. Second, as per PANIS guidelines (Devlin et al., 2018) IV sedation requires a daily sedation interruption whereas inhaled sedation does not due to continuous monitoring. Daily sedation interruption (DSI) has been proposed as a method of improving sedation management of critically ill patients by reducing the adverse effects of continuous sedation infusions.

For IV sedation, the selected dose intensity will also determine the rate of vial usage over time and the frequency of required infusion pump syringe change. In the base-case for propofol this equates to approximately 10 infusion syringes per 24 hours. The model includes a nominal unit cost of supply and disposal of infusion syringes and allocates the cost of nurse time for dose renewal/ infusion syringe change (base case assumption is 6mins per change x10 = 60 mins, assigned labour cost of £20 per patient per 24 hours sedation). In the base-case the duration of DSI for IV sedation is 30minutes and involves 2 ICU nurses (assigned labour cost of £20 per patient per 24 hours sedation). Assigned costings are conservative.

For AnaConDa, unit drug cost is taken from BNF (ISOFLURANE | Medicinal forms | BNF content published by NICE) supplied as 250ml bottles. Costs for device equipment and accessories is provided by Sedana Medical (data on file). A total cost per patient is provided in the model based on the unit cost of each component and its required rate of replacement.

For ICU costs the model uses the NHS Reference costs. For an ICU bed day with mechanical ventilation a unit cost of £1,218 is used (NHS Reference Costs. Main Schedule. 2018/19. National average unit cost for critical care). For a non-ventilated ICU bed day a unit cost of £933 is used (NHS Reference Costs. Main Schedule. 2018/9. CCU01 Non-specific, general adult critical care patients predominate. Adult Critical Care, 0 Organs Supported). These costs are conservative.

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

N/A

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
Adverse event 1	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
Adverse event 2	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
[Add more rows as needed]			

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

none

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Less drug changes so a reduced potential risk for drug errors. Less nursing time away from the bedside. The drug is not controlled so can be kept by the bed and syringe change is much less due to low rates of infusion. Less time to ween patients who have been sedated for long periods.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost (based on SED001)	Component Unit cost	Renewal rate	Source
[redacted]	[redacted]	[redacted]	24hours Single use Single use 4 days 4 days 4 days 900 days 1 per patient	Sedana Medical 2021 price list applied to SED001 clinical data, [redacted] days sedation in ICU

		[redacted]		
Training cost over lifetime of device	Sedana Medical provide support and online resources: E-learning, AnaConDa User Guide (Home - Sedana Medical)			
Other costs per year and over lifetime of device	**£111**	Isoflurane 250ml £35.29	3ml/hour	BNF
Total cost per treatment/patient over lifetime of device	**£1,044**			

Table 8 Total costs for the comparator in the model

N/A – SoC sedation is IV drug (such as propofol) as costed above. No comparator technology.

Results

Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Table 9 Base case (clinical data from RCT SED001)

	Propofol	**Isoflurane via AnaConDa**	**Delta**
Mean sedation cost per episode	£774	[redacted]	[redacted]
Mean duration of ICU stay (days)	[redacted]	[redacted]	[redacted]
Mean duration of MV (days)	[redacted]	[redacted]	0
Cost per ICU stay	£18,874	£14,956	-£3,919
Net Cost per patient			***-£3,649*** (saving per patient)

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

- Describe the differences between the base case and each scenario analysis.
- Describe how the scenario analyses were included in the cost analysis.
- Describe the evidence that justifies including any scenario analyses.

As discussed in the clinical submission (part 1), RCTs in ICU sedation inherently have design issues (e.g. short randomised periods) that make comparison of overall ICU length-of-stay and time on a ventilator challenging. The base case analysis (Table 9) characterises the observed statistically significant difference in duration of ICU stay based on the 30day follow-up of non-switching patients but since the difference between the groups in duration of mechanical ventilation was not statistically significant [redacted] the mean duration across both groups was applied, assuming no difference. Table 10a details the scenario analysis that assumes that this observed trend [redacted] is the difference is duration of mechanical ventilation between the two groups.

UK standard-of-care sedation is primarily IV propofol and/or IV midazolam (IV dexmedetomidine is licensed but less widely used in this context). Propofol is more commonly used, however, the choice of propofol or midazolam may depend on the clinical context and expected duration of sedation needed. Longer-term use of propofol may be avoided due to accumulation and tolerance issues whereas the use of midazolam may bring issues known to be associated with benzodiazepines. In some patients both IV strategies maybe used sequentially. In order to be most informative to HTA decision-makers a scenario analysis comparing isoflurane via AnaConDa with midazolam is also presented (Table 10b).

Finally, Table 10c presents a scenario analysis that uses all available 30day follow-up data from RCT SED001 without controlling for those that switched sedation regimen after the 48h randomised study period. There were [redacted] patients from the isoflurane group who switched to propofol at some time point from last dose of study sedation until day 30. Similarly, there were [redacted] patients from the propofol group who switched to isoflurane at some time point from last dose of study sedation until day 30. Differences between the groups in ICU and mechanical ventilation duration are not statistically significant but are costed to illustrate this scenario.

Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

Table 10a Scenario analysis vs. Propofol (assuming difference in duration of mechanical ventilation as in SED001 (non-switchers))

	Propofol	**Isoflurane via AnaConDa**	**Delta**
Mean sedation cost per episode	£845	[redacted]	[redacted]
Mean duration of ICU stay (days)	[redacted]	[redacted]	[redacted]
Mean duration of MV (days)	[redacted]	[redacted]	[redacted]
Cost per ICU stay	£19,159	£14,557	-£4,603
Net Cost per patient			***-£4,498*** (saving per patient)

Table 10b Scenario analysis vs. Midazolam (clinical data based on Krannich et al. 2017, observational study)

	Midazolam	**Isoflurane via AnaConDa**	**Delta**
Mean sedation cost per episode	£598	£674	£75
Median duration of ICU stay (days)	13	8	-5
Median duration of MV (days)	11.2	7.1	-4.1
Cost per ICU stay	£15,321	£9,488	-£5,834
Net Cost per patient			***-£5,759*** (saving per patient)

Table 10c Scenario analysis vs. Propofol (assuming difference in duration of mechanical ventilation and ICU duration as in SED001 [redacted]

	Propofol	**Isoflurane via AnaConDa**	**Delta**
Mean sedation cost per episode	£924	[redacted]	[redacted]
Mean duration of ICU stay (days)	[redacted]	[redacted]	[redacted]
Mean duration of MV (days)	[redacted]	[redacted]	[redacted]
Cost per ICU stay	£20,219	£18,864	-£1,355
Net Cost per patient			***-£1,035*** (saving per patient)

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Sensitivity analysis is performed on each of the clinical and cost parameters in the model as a one-way sensitivity analysis.

In addition, threshold sensitivity analysis is performed to show the required values for key parameters in order for net cost impact to be neutral (breakeven).

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Each of the following parameters was varied +/- 20% from base case inputs:

- Overall sedation costs (drug & non-drug) - Isoflurane via AnaConDa
- Overall sedation costs (drug & non-drug) – Propofol
- Unit cost per ICU day (non-ventilated)
- Unit cost per ICU day (mechanical ventilation)
- Duration of mechanical ventilation - Isoflurane via AnaConDa (ICU episode duration increases the same)
- Duration of mechanical ventilation – Propofol (ICU episode duration increases the same)
- Duration of ICU (non-mechanical ventilation) - Isoflurane via AnaConDa (ICU episode duration increases the same)
- Duration of ICU (non-mechanical ventilation) – Propofol (ICU episode duration increases the same)

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

N/A

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

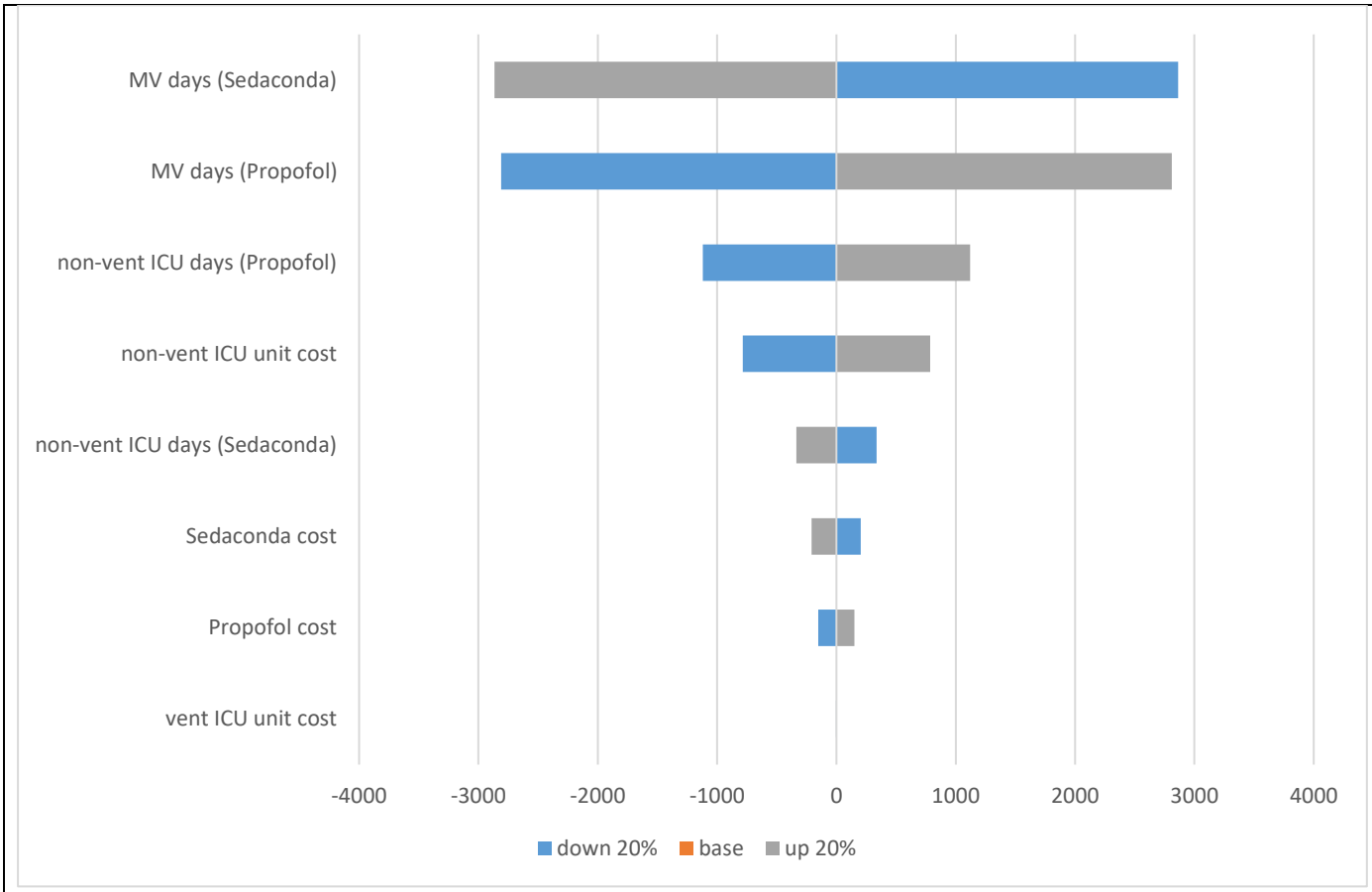
Table 11 shows the results of one-way sensitivity analysis. Each parameter is varied +/-20% to show impact on the base case model result.

Table 11: One-way sensitivity analysis

Parameter	OWSA			Net cost per sedated patient (savings)		
	-20%	base	+20%	-20%	base	+20%
Propofol cost	£57	£71	£85	£3,496	£3,649	£3,801
Sedaconda cost	£77	£96	£115	£3,854		£3,440
non-vent ICU unit cost	£746	£933	£1,120	£2,864		£4,435
vent ICU unit cost	£974	£1,218	£1,462	£3,649		£3,649
non-vent ICU days (Propofol)	[redacted]	[redacted]	[redacted]	£2,530		£4,769
MV days (Propofol)	[redacted]	[redacted]	[redacted]	£839		£6,459
non-vent ICU days (Sedaconda)	[redacted]	[redacted]	[redacted]	£3,985		£3,313
MV days (Sedaconda)	[redacted]	[redacted]	[redacted]	£6,513		£785

Sedaconda = isoflurane via AnaConDa

These results are shown on the tornado plot below.



Threshold sensitivity analyses shows that if the duration of mechanical ventilation is set as equal for both isoflurane via AnaConDa and propofol ([redacted] then the duration of non-ventilation ICU days needs to be a delta of 0.33 days lower for isoflurane via AnaConDa for the model to show zero net cost impact in order to offset the slightly higher sedation costs.

What were the main findings of each of the sensitivity analyses?

The base case analysis showed net cost savings per sedated patient (£3,649) in favour of isoflurane via AnaConDa compared to IV propofol sedation. One-way sensitivity analysis shows that when independently varying eight parameters +/-20%, isoflurane via AnaConDa remains cost saving compared to propofol in all cases.

What are the main sources of uncertainty about the model's conclusions?

The model is most sensitive to estimates of ICU duration and particularly the time spent on the ventilator since this has the highest unit costs and determines the duration of sedation required. Varying the unit cost of ventilator ICU days alone has no impact as the base case explicitly set the duration of ventilator days equal across the two groups.

Miscellaneous results

Include any other relevant results here.

N/A

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

The economic base case analysis presented here uses a simple cost-consequence model, applying UK NHS costs to clinical parameters generated by RCT SED001, the largest study of its kind directly comparing sedation of adult mechanically ventilated patients in ICU using isoflurane via AnaConDa or IV propofol. The clinical evidence used in the base case is consistent with external evidence generated by the clinical SLR (Table 12, Table 13). Whereas the studies by Rohm et al., 2009, 2008 have shown a statistically significant reduction in duration of mechanical ventilation in ICU (Sevoflurane/AnaConDa vs. propofol) other studies have shown comparable durations or trends in favour of inhaled sedation without reaching statistical significance. For the duration of ICU stay, all clinical evidence shows comparable durations or trends in favour of inhaled sedation without reaching statistical significance, except the SED001 post-hoc analyses that is significantly in favour of isoflurane. One-hour interviews were conducted with HTA/ Health Economic KoLs from EU4 and the UK to review both the clinical and economic analyses.

Table 12: Summary of evidence comparing duration of mechanical ventilation in ICU – inhaled sedation vs Propofol

Source of evidence	Study Name	Findings
[redacted]	[redacted]	[redacted]
SLR	Hellström et al., 2012 (N=99)	Comparable, NS
SLR	Mesnil et al., 2011 (N=47)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NS
SLR	Rohm et al., 2009 (N=126)	In favour of inhaled (sevoflurane) via AnaConDa, p<0.009
SLR	Rohm et al., 2008 (N=70)	In favour of inhaled (sevoflurane) via AnaConDa, p=0.0001
Review of Observational Studies	Staudacher et al., 2018 (N=214)	Comparable, NS

Table 13: Summary of evidence comparing duration of ICU stay – inhaled sedation vs Propofol

Source of evidence	Study Name	Findings
[redacted]	[redacted]	[redacted]
SLR	Jerath et al., 2015 (N=141)	Comparable, NS
SLR	Marcos-Vidal et al., 2014 (N=129)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NS
SLR	Soro et al., 2012 (N=73)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NS
SLR	Steurer et al., 2012 (N=102)	Comparable, NS
SLR	Hellström et al., 2012 (N=99)	Comparable, NS
SLR	Mesnil et al., 2011 (N=47)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NS
SLR	Rohm et al., 2009 (N=126)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NK
SLR	Rohm et al., 2008 (N=70)	Trend in favour of inhaled (sevoflurane) via AnaConDa, NS
Review of Observational Studies	Staudacher et al., 2018 (N=214)	Trend in favour of isoflurane via AnaConDa, NS

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

A draft version of the model was demonstrated to:

Dr Mark Blunt, lead critical care consultant, The Queen Elizabeth Hospital King's Lynn.

The potential resource savings associated with less sedation dose renewal (vs. Propofol) and the role of DSI (daily sedation interruption) protocol were highlighted by Dr Blunt.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Only two studies (Sackey et al., 2018; L'Her et al., 2008) were considered potentially directly relevant to the decision problem that included inhaled sedation. Both studies found economic advantages for inhaled sedation. A de novo cost-consequence analysis was developed based on a decision-analytic model.

The base case analysis is populated by data from the SED001 RCT. Mean sedation costs (drugs, equipment, consumables, administration, and monitoring) are found to be slightly higher per patient episode for isoflurane via AnaConDa compared to propofol (£1,044 vs. £774 per patient episode). Mean ICU costs are lower for isoflurane via AnaConDa compared to propofol (£14,956 vs. £18,874) based on a statistically significant difference in mean ICU length of stay [redacted] but assuming no difference in the duration of mechanical ventilation. This results in an overall net cost saving of £3,649 per patient episode for isoflurane via AnaConDa compared to propofol. A range of scenario and sensitivity analyses continue to show net cost savings per patient episode in favour of isoflurane via AnaConDa.

Briefly discuss the relevance of the evidence base to the scope.

The economic evidence presented here is aligned to the decision problem included in the scope. The population are people who are invasively ventilated in intensive care using a mechanical ventilator and requiring sedation. The intervention (AnaConDa, delivering isoflurane) is compared to IV sedatives (primarily propofol). The duration of mechanical ventilation and the duration of time spent in ICU are of course both patient-relevant and health-system relevant endpoints. The economic analyses presented here are focussed on the potential for net cost savings for the NHS. The benefit to patients of faster wake-up, cognitive recovery, less time spent in ICU and potentially less time on a ventilator are also important consequences to be considered.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Tables 12 and 13 (above) show how the key clinical data used in this analysis aligns with studies identified from the clinical SLR. Results are consistent with published literature.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The RCT SED001 [redacted] included a wide range of patient groups as the inclusion criteria were kept broad: male or female subjects, >=18 years; continuous invasive ventilation and sedation <=48 hours at start of study sedation; clinically likely to need invasive ventilation and sedation >=24 hours at randomisation; ongoing sedation with propofol at time of randomisation; [redacted] Hence the cost analysis presented here is intended to apply to all these patient groups, in need of sedation to support them whilst receiving mechanical ventilation in the ICU. No analysis of patient sub-groups was attempted. The evidence presented is relevant to patients identified in the scope.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The key strength of this cost analysis is that it is based on clinical data from SED001, the largest RCT of its kind. This analysis supports the established clinical view that inhaled sedation should facilitate better clinical flexibility in managing ventilated ICU patients and shows that the ICU stay can be significantly shortened. The consequences for the patients and the costs for the NHS are better than IV sedation.

The main potential limitation of this cost analysis is that the base case uses a post-hoc analysis of the 30day follow-up data for duration of mechanical ventilation and ICU stay. A total of [redacted] patients were included in SED001, complete data on 30day follow-up was available for a total of [redacted] patients. A pre-specified analysis compared 30day data by randomised group allocation (for the 48+/-6h randomised study period), although the protocol specified that after 48+/-6h the sedation could continue according to local practice as deemed necessary by the treating physician.

[redacted]

Detail any further analyses that could be done to improve the reliability of the results.

AnaConDa has demonstrated clinical and economic benefits for the sedation of a wide range of patients based on SED001. The cost-consequence model has made the simplifying assumption that sedation efficacy, tolerability and safety is not different between the intervention and comparator(s) (based on non-inferiority design of RCT SED001). Further analyses could explore potential reasons to relax this assumption. There has been some interest in the potential therapeutic value of inhaled sedation for patients with specific respiratory conditions (ARDS, bronchospasm etc.). Although RCT SED001 was not designed to show differences for these specific subgroups, further analyses could be pursued to illustrate potential gains for these patient sub-groups.

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Please include all references below using NICE's standard referencing style.

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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Table 14: Summary protocol for economic evaluations targeted literature review (TLR)

Criteria	Details	
Population	• Mechanically ventilated adult patients (>18 years) requiring sedation	
Interventions	• Desflurane • Isoflurane • Sevoflurane • Propofol • Haloperidol	• Dexmedetomidine • Clonidine • Midazolam • Lorazepam • Morphine
Comparators	• No restriction	
Outcomes*	Key outcomes including: • Incremental cost-effectiveness ratio (ICER) • Type of perspective (Third-party, payer, etc.) • Type of resources evaluated (emergency room, nursing facility, etc.) • Type of costs measured • Source of costs • Cost year	
Study design	• Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis	• Cost minimization analysis • Budget impact models • Cost-consequence studies
Data sources	Biomedical databases: • Embase® and MEDLINE® (Using Embase.com) • MEDLINE In-Process (Using PubMed interface) • NHS Economic Evaluation Database (NHS EED)** Conferences (last three years) • International Society for Pharmacoeconomics and Outcomes Research (ISPOR): International, Asia, and Europe Other sources • Bibliography of relevant systematic reviews • Hand searching of Tufts cost-effectiveness registry	
Timeframe	• Last 15 years (2006-2020) to include the latest evidence	
Language	• English language studies only	
Methodology	• TLR will follow a single review process for data collection and extraction	
Critical appraisal	• The critical appraisal of economic studies will be carried out using the adapted Drummond's checklist as recommended in the NICE single technology appraisal (STA) manufacturer's template[1] • The validity of the economic model studies reporting data of interest will be assessed using Philips checklist[2]	
Deliverables	• List of included studies (MS Excel) • Data tables (MS Excel)	

[1] Drummond, M.F. and T.O. Jefferson, Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ, 1996. 313(7052): p. 275-83.
[2] Philips, Z., et al., *Review of guidelines for good practice in decision-analytic modelling in health technology assessment.* Health Technol Assess, 2004. **8**(36): p. iii-iv, ix-xi, 1-158.

Table 15: Search strategy for Embase® and MEDLINE® using Embase.com

S. No	Query	Hits
1	'conscious sedation'/exp	7,627
2	'artificial ventilation'/exp	205,203
3	'artificial respiration' OR 'controlled respiration' OR 'controlled ventilation' OR 'mechanical respiration' OR 'mechanical ventilation' OR ventilat* OR 'anesthesia conserving device' OR 'anaesthesia conserving device'	329,414
4	'intensive care'/exp OR icu:ab,ti	766,762
5	(mechanical* OR artificial*) NEAR/5 ventilat*	162,103
6	'critical illness' OR 'critical care'	384,188
7	#2 OR #3 OR #4 OR #5 OR #6	1,038,360
8	sedation:ab,ti OR sedat*:ab,ti	87,989
9	#1 OR (#7 AND #8)	28,432
10	'economics'/exp OR 'economics'/de OR 'economic aspect'/exp OR 'economic aspect'/de OR 'cost'/exp OR 'cost'/de OR 'health care cost'/exp OR 'health care cost'/de OR 'drug cost'/exp OR 'drug cost'/de OR 'hospital cost'/exp OR 'hospital cost'/de OR 'socioeconomics'/exp OR 'socioeconomics'/de OR 'health economics'/exp OR 'health economics'/de OR 'pharmacoeconomics'/exp OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'hospital finance'/exp OR 'hospital finance'/de OR 'financial management'/exp OR 'financial management'/de OR 'health care financing'/exp OR 'health care financing'/de OR 'low cost' OR 'high cost' OR (health*care NEXT/1 cost*) OR ('health care' NEXT/1 cost*) OR fiscal OR 'funding'/exp OR funding OR financial OR 'finance'/exp OR finance OR (cost NEXT/1 estimate*) OR 'cost variable' OR (unit NEXT/1 cost*) OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR ((cost* NEAR/3 (treat* OR therap*)):ab,ti) OR (((direct OR indirect) NEAR/2 cost*):ab,ti) OR 'cost effectiveness analysis'/syn OR 'cost benefit analysis'/syn OR 'cost utility analysis'/syn OR 'cost minimization analysis'/syn OR 'economic evaluation'/syn OR 'budget impact analysis'/syn OR ((economic OR 'cost-benefit' OR 'cost-effectiveness' OR 'cost-utility' OR 'budget-impact') NEXT/1 (evaluation* OR analys* OR model* OR intervention*)) OR (('cost minimization' OR 'cost minimisation') NEXT/1 (analys* OR model*)) OR (economic NEXT/1 (evaluation* OR model)) OR ('health*care' NEXT/1 (utilisation OR utilization)) OR ('health care' NEXT/1 (utilisation OR utilization)) OR (resource NEXT/1 (utilisation OR utilization OR use))	2,120,267
11	#9 AND #10	1,827
12	'desflurane'/exp OR 'desflurane'/syn OR 'i 653':ab,ti OR sulorane:ab,ti OR suprane:ab,ti OR 'isoflurane'/exp OR 'isoflurane'/syn OR forane:ab,ti OR forene:ab,ti OR forthane:ab,ti OR isoflurano:ab,ti OR isorane:ab,ti OR sofloran:ab,ti OR 'sevoflurane'/exp OR 'sevoflurane'/syn OR sevocalm:ab,ti OR sevoflo:ab,ti OR sevofrane:ab,ti OR sevohale:ab,ti OR sevorane:ab,ti OR sevotec:ab,ti OR sojourn:ab,ti OR ultane:ab,ti OR 'dexmedetomidine'/exp OR 'dexmedetomidine'/syn OR cepedex:ab,ti OR dexamedetomidine:ab,ti OR dexdomitor:ab,ti OR dexdor:ab,ti OR 'dexmedetomidine hydrochloride':ab,ti OR 'mpv 1440':ab,ti OR 'mpv1440':ab,ti OR precedex:ab,ti OR primadex:ab,ti OR sedadex:ab,ti OR sileo:ab,ti OR 'clonidine'/exp OR 'clonidine'/syn OR clonidine:ab,ti OR clofenil:ab,ti OR klofenil:ab,ti OR m5041t:ab,ti OR 'm 5041t':ab,ti OR catapres*:ab,ti OR 'st155':ab,ti OR 'st 155':ab,ti OR 'propofol'/exp OR 'propofol'/syn OR cryotol:ab,ti OR diisoprofol:ab,ti OR diprivan:ab,ti OR diprofol:ab,ti OR disoprivan:ab,ti OR disoprofol:ab,ti OR fresofol:ab,ti OR gobbifol:ab,ti OR 'ici 35 868':ab,ti OR 'ici 35868':ab,ti OR plofed:ab,ti OR pofol:ab,ti OR profast:ab,ti OR propocam:ab,ti OR 'propofol lipuro':ab,ti OR 'propofol-lipuro':ab,ti OR 'propolipid':ab,ti OR 'propoven':ab,ti OR 'provive':ab,ti OR apinovet:ab,ti OR rapiva:ab,ti OR recofol:ab,ti OR 'recofol	195,837

	n':ab,ti OR 'midazolam'/exp OR 'midazolam'/syn OR midacum:ab,ti OR midafresa:ab,ti OR midazo:ab,ti OR midazol:ab,ti OR 'midazolam hydrochloride':ab,ti OR midolam:ab,ti OR miloz:ab,ti OR nayzilam:ab,ti OR 'nvd 301':ab,ti OR 'nvd301':ab,ti OR 'ro 21 3981':ab,ti OR 'ro 21-3981':ab,ti OR 'ro 21-3981-003':ab,ti OR 'ro 213981':ab,ti OR 'ro 213981003':ab,ti OR 'ro21 3981':ab,ti OR 'ro21 3981 003':ab,ti OR 'ro21-3981':ab,ti OR 'ro21-3981-003':ab,ti OR 'ro213981':ab,ti OR 'ro213981003':ab,ti OR 'seizalam':ab,ti OR 'shp 615':ab,ti OR 'shp615':ab,ti OR 'suda 003':ab,ti OR 'suda003':ab,ti OR 'usl 261':ab,ti OR 'usl261':ab,ti OR versed:ab,ti OR 'lorazepam'/exp OR 'lorazepam'/syn OR almazine:ab,ti OR alzapam:ab,ti OR anxiedin:ab,ti OR anxira:ab,ti OR anzepam:ab,ti OR aplacasse:ab,ti OR 'apo lorazepam':ab,ti OR aripax:ab,ti OR ativan:ab,ti OR azurogen:ab,ti OR bonatranquan:ab,ti OR duralozam:ab,ti OR efasedan:ab,ti OR emotival:ab,ti OR kalmalin:ab,ti OR kendol:ab,ti OR larpose:ab,ti OR laubeel:ab,ti OR lonza:ab,ti OR lopam:ab,ti OR lorabenz:ab,ti OR loram:ab,ti OR loranase:ab,ti OR loranaze:ab,ti OR lorans:ab,ti OR lorapam:ab,ti OR loravan:ab,ti OR lorax:ab,ti OR loraz:ab,ti OR lorazene:ab,ti OR lorazep:ab,ti OR 'lorazepam intensol':ab,ti OR lorazin:ab,ti OR lorazon:ab,ti OR lorenin:ab,ti OR loridem:ab,ti OR lorivan:ab,ti OR lorsedal:ab,ti OR lorzem:ab,ti OR merlit:ab,ti OR mesmerin:ab,ti OR 'nervistop l':ab,ti OR novhepar:ab,ti OR 'novo lorazem':ab,ti OR orfidal:ab,ti OR orifadal:ab,ti OR placinoral:ab,ti OR 'pro dorm':ab,ti OR punktyl:ab,ti OR quait:ab,ti OR renaquil:ab,ti OR rocosgen:ab,ti OR securit:ab,ti OR sinestron:ab,ti OR stapam:ab,ti OR tavor:ab,ti OR temesta:ab,ti OR titus:ab,ti OR tranqipam:ab,ti OR trapax:ab,ti OR trapex:ab,ti OR 'wy 4036':ab,ti	
13	#11 AND #12	734
14	#13 AND [2006-2020]/py (Applying limits; last 15 years)	554

Searched on 17 July 2020

Table 16: Search strategy for MEDLINE® In-Process searched via PubMed® platform

S. No	Query	Hits
1	"conscious sedation"[MeSH Terms]	8,884
2	"conscious sedation"	10,413
3	artificial ventilation[MeSH Terms]	76,788
4	"artificial ventilation" OR "artificial respiration" OR "controlled respiration" OR "controlled ventilation" OR "mechanical respiration" OR "mechanical ventilation" OR ventilat* OR “anesthesia conserving device” OR “anaesthesia conserving device”	202,697
5	"intensive care"	2,53,745
6	intensive care[MeSH Terms]	57,735
7	icu[Title/Abstract]	56,439
8	(mechanical* OR artificial*) AND ventilat*	79,779
9	"critical illness" OR "critical care"	2,05,262
10	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	559,484
11	sedation OR sedat*	78,444
12	#10 AND #11	12,280
13	#1 OR #2	10,365
14	#12 OR #13	21,754

15	desflurane OR "i 653" OR sulorane OR suprane OR isoflurane OR forane OR forene OR forthane OR isoflurano OR isorane OR sofloran OR sevoflurane OR sevocalm OR sevoflo OR sevofrane OR sevohale OR sevorane OR sevotec OR sojourn OR ultane OR dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR "dexmedetomidine hydrochloride" OR "mpv 1440" OR "mpv1440" OR precedex OR primadex OR sedadex OR sileo OR clonidine OR clofenil OR klofenil OR m5041t OR "m 5041t" OR catapres* OR "st155" OR "st 155" OR propofol OR cryotol OR diisoprofol OR diprivan OR diprofol OR disoprivan OR disoprofol OR fresofol OR gobbifol OR "ici 35 868" OR "ici 35868" OR plofed OR pofol OR profast OR propocam OR "propofol lipuro" OR propofol-lipuro OR propolipid OR propoven OR provive OR apinovet OR rapiva OR recofol OR "recofol n" OR midazolam OR midacum OR midafresa OR midazo OR midazol OR "midazolam hydrochloride" OR midolam OR miloz OR nayzilam OR nvd301 OR lorazepam OR almazine OR anxiedin OR anxira OR anzepam OR aplacasse OR "apo lorazepam" OR aripax OR ativan OR azurogen OR bonatranquan OR duralozam OR efasedan OR emotival OR kalmalin OR larpose OR laubeel OR lonza OR lopam OR lorabenz OR loram OR lorans OR lorapam OR lorax OR loraz OR lorazene OR lorazep OR "lorazepam intensol" OR lorazin OR lorazon OR lorenin OR loridem OR lorivan OR lorsedal OR lorzem OR merlit OR "nervistop l" OR novhepar OR orfidal OR "pro dorm" OR punktyl OR quait OR renaquil OR rocosgen OR securit OR sinestron OR stapam OR temesta OR tranqipam OR trapax OR trapex	79,376
16	#14 AND #15	7,599
17	cost effectiveness[MeSH Terms] OR "cost effectiveness analysis" OR "cost utility analysis" OR economic model[MeSH Terms] OR "economic evaluation" OR cost benefit analysis[MeSH Terms] OR “cost benefit analysis” OR monte carlo method[MeSH Terms] OR markov chain[MeSH Terms] OR "monte carlo" OR "montecarlo" OR markov*	183,085
18	("cost efficiency analysis" OR (("cost-efficiency") AND (evaluation* OR analys* OR model* OR modeling OR modelling OR model OR method* OR simulation* OR assessment*)))	1,916
19	(economic OR "cost-benefit" OR "cost-effectiveness" OR "cost-utility") AND (evaluation* OR analys* OR model* OR method* OR simulation* OR assessment*)	581,107
20	"cost minimization analysis"	549
21	("cost minimization" OR "cost minimisation") AND (analys* OR model* OR simulation* OR assessment*)	1,219
22	("budget impact") AND (analys* OR model* OR simulation* OR assessment*)	1,348
23	Cost AND (evaluation* OR analys* OR model* OR simulation* OR assessment*)	449,620
24	cost[MeSH Terms]	236,869
25	economics OR "economic aspect" OR "socioeconomics" OR "health economics" OR "pharmacoeconomics" OR "cost variable" OR "unit cost" OR "resource utilisation" OR "resource utilization" OR "resource use" OR "treatment cost" OR "therapy cost"	996,938
26	“cost”[Title/Abstract] OR “health care cost”[Title/Abstract] OR “drug cost”[Title/Abstract] OR “hospital cost”[Title/Abstract] OR “fee”[Title/Abstract] OR “budget”[Title/Abstract] OR “low cost”[Title/Abstract] OR “high cost”[Title/Abstract] OR economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract] OR price*[Title/Abstract] OR pricing[Title/Abstract] OR “health care utilization”[Title/Abstract] OR “health care utilisation”[Title/Abstract] OR “direct cost”[Title/Abstract] OR “indirect cost”[Title/Abstract]	715,042
27	Cost AND (treat* OR therap* OR treatment OR therapy OR direct OR indirect)	408,282
28	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	1,366,570
29	#16 AND #28	338
30	#29 AND (inprocess[sb] OR pubstatusaheadofprint)	10

Searched on 17 July 2020

Table 17: Search strategy for NHS EED searched via York CRD

S. No	Query	Hits
1	"conscious sedation" OR "intensive care" OR "artificial ventilation" OR ventilat* OR "artificial respiration" OR "controlled respiration" OR "controlled ventilation" OR "mechanical respiration" OR "mechanical ventilation"	1,033
2	desflurane OR "i 653" OR sulorane OR suprane OR isoflurane OR forane OR forene OR forthane OR isoflurano OR isorane OR sofloran OR sevoflurane OR sevocalm OR sevoflo OR sevofrane OR sevohale OR sevorane OR sevotec OR sojourn OR ultane OR dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR "dexmedetomidine hydrochloride" OR "mpv 1440" OR "mpv1440" OR precedex OR primadex OR sedadex OR sileo OR clonidine OR clofenil OR klofenil OR m5041t OR "m 5041t" OR catapres* OR "st155" OR "st 155" OR propofol OR cryotol OR diisoprofol OR diprivan OR diprofol OR disoprivan OR disoprofol OR fresofol OR gobbifol OR "ici 35 868" OR "ici 35868" OR plofed OR pofol OR profast OR propocam OR "propofol lipuro" OR propofol-lipuro OR propolipid OR propoven OR provive OR apinovet OR rapiva OR recofol OR "recofol n" OR midazolam OR midacum OR midafresa OR midazo OR midazol OR "midazolam hydrochloride" OR midolam OR miloz OR nayzilam OR nvd301 OR lorazepam OR almazine OR anxiedin OR anxira OR anzepam OR aplacasse OR "apo lorazepam" OR aripax OR ativan OR azurogen OR bonatranquan OR duralozam OR efasedan OR emotival OR kalmalin OR larpose OR laubeel OR lonza OR lopam OR lorabenz OR loram OR lorans OR lorapam OR lorax OR loraz OR lorazene OR lorazep OR "lorazepam intensol" OR lorazin OR lorazon OR lorenin OR loridem OR lorivan OR lorsedal OR lorzem OR merlit OR "nervistop l" OR novhepar OR orfidal OR "pro dorm" OR punktyl OR quait OR renaquil OR rocosgen OR securit OR sinestron OR stapam OR temesta OR tranqipam OR trapax OR trapex	149
3	#1 AND #2	49
4	#3 (2011 to 2020)	7

Searched on 17 July 2020

Table 18: Combined hits from all databases

S. No	Database	Hits
1	Embase® and MEDLINE®	554
2	MEDLINE® In-Process	10
3	CENTRAL	7
4	Total	571

A total of 20 manuscripts were selected for full data extraction, a full list is provided here:

TLR in MV_List of included studies_Eco

A data workbook was developed for these studies:

TLR for sedation of mechanically ventilat

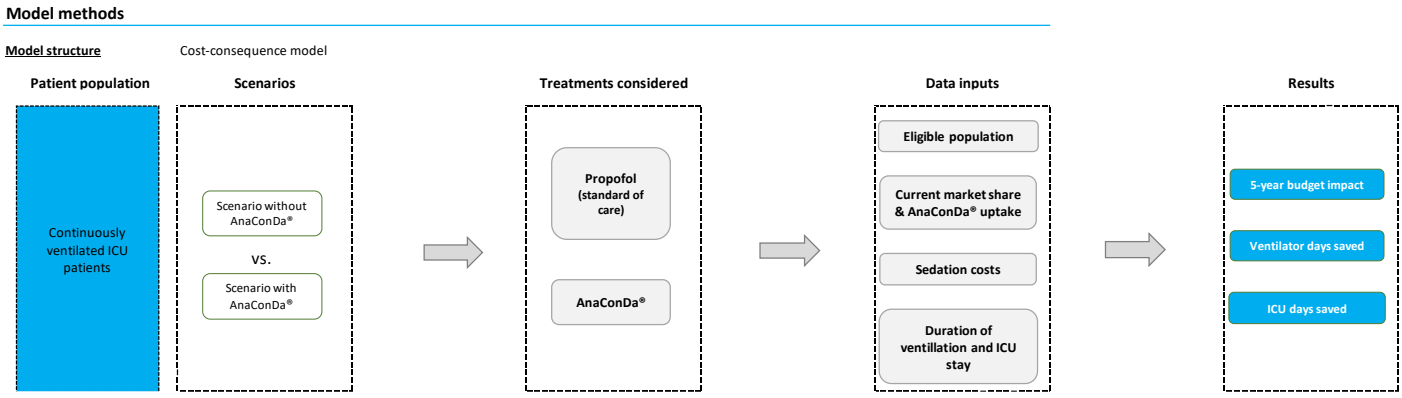
For the NICE decision problem, only 2 manuscripts from this workbook were considered directly relevant: L'Her et al. 2008, Sackey et al. 2018.

During this review of economic evidence, studies considered of relevance to inform resource identification, measurement and valuation were also collated. Some 40 relevant studies are listed here:

TLR in MV_List of included studies_Cos

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

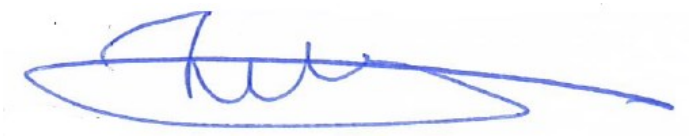
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
12/13	☒ Commercial in confidence ☐ Academic in confidence Details: Enter text.	Commercial price data	Enter text.
19	☒ Commercial in confidence ☐ Academic in confidence Details: Enter text.	Commercial price data	Enter text.

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	25th May 2021
Print:	Jens Lindberg	**Role / organisation:**	VP Commercial Operations

Contact email: Jens.Lindberg@sedanamedical.com

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	Dr Stephen Playfor, Consultant Paediatric Intensivist, Manchester University NHS Foundation Trust,
	Nominated by: NICE
	DOI: YES I have been asked by Sedana Medical to participate in an online workshop at some point later in 2020 to discuss my experience of using the AnaConDa system. I am not anticipating being offered any sort of fee to speak, but it might be considered to enhance my professional standing
Expert #2	Professor Anil Hormis, Consultant in Anaesthesia & Critical Care Medicine, Rotherham NHS Foundation Trust,
	Nominated by: Company
	DOI: Direct - financial Honoraria received from Teleflex : lectures / teaching (No conflict declared) Direct - financial Honoraria received from Medtronic : lectures / teaching (No conflict declared)
Expert #3	Dr Jonathan Ball, Consultant in intensive care medicine, St George's University Hospitals NHS Foundation Trust,
	Nominated by : NICE
	DOI: N/A
Expert #4	Dr Guy Glover, Consultant in Anaesthesia & Critical Care, Guy's and St Thomas NHS Foundation Trust,
	Nominated by: Company
	DOI: Attended an Anaconda study day, sponsored by Sedana, Sept 2019
Expert #5	Dr Mark Blunt, Lead Critical Care Consultant, The Queen Elizabeth Hospital King's Lynn,
	Nominated by: Company
	DOI: NONE
Expert #6	Paul Dean, Consultant , East Lancashire Hospitals NHS Trust, Click here to enter text.
	Nominated by: ICS

	DOI: NONE
Expert #7	Thomas Syratt, ST8 in anaesthetics/intensive care medicine,
	Nominated by: ICS
	DOI: NONE

			Response
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this	Expert #1: We had been using the original AnaConDa device regularly in my PICU for around 12 years, probably once a month on average. We have now moved to the AnaConDa-S device since it became available	
		Expert #2 Yes – I am very familiar with the technology. We have used it on the ICU for 10 months now. We are very used to using isoflurane in the operating theatres. Yes I have used AnaConDa in a number of patients – and we are still currently using it for sedation on the ICU – 5 of our bed spaces have the gas monitoring capability now and we have 1 mobile gas monitor available for use.	

	procedure/technology, please indicate your experience with it.	I have not done any research into AnaConDa / Isoflurane in the critical care setting. I have not been involved in its development It is not widely used in the NHS – Our unit is the only ICU in our region that uses it routinely for sedation on the ICU	
		Expert #3 I'm familiar with volatile anaesthetics but not this particular delivery system	
		Expert #4 Currently undertaking an evaluation, accelerated by Covid-19 pandemic when it was promoted as a potential alternative in the face of IV sedation shortages. Expereince limited to approx. 10 cases Not involved currently in R & D Limited to a small number of hospitals – I would estimate < 20 to the best of my knowledge	
		Expert #5 I have been using this technology for the last 6 months or so, and we are continuing to use it. We are presently using it on approximately 5 patients per month and continue to evaluate the relative	

		benefits, as there is relatively little data available to ascertain its utility. My understanding is that there are a small but increasing number of users within the UK (I know of 3 (~15% of units) hospitals using it at present.	
		Clinically used this device. I am familiar with the procedure / technology. Used predominantly within adult critical care units only.	
		Expert #7 Personally I have not used this piece of equipment in clinical practice. I have used volatile anaesthetics in the treatment of near fatal asthma, though this has been confined to the use of anaesthetic vaporizers via a designated anaesthetic machine. With regard to the wider use of this technology, most trainees asked were aware of the technology but had not used the system. They were aware of the system and knew of trusts that had trialled the equipment or had used it on occasion.	

		Many intensive care trainees and consultants are from an anaesthetic background and all will have been through an anaesthetic placement. The use of volatile anaesthetics is obviously common place in this speciality and therefore gives some familiarity with their use. In trusts I have worked in, if it was thought that volatile anaesthetics would benefit the patient then the patient would either be moved to the anaesthetic department to deliver them or the anaesthetic machine moved to the patient.	
		Expert #8	
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	

		Expert #6 I have had no involvement in research on this procedure. Other (please comment)	
		Expert #7 I have had no involvement in research on this procedure.	
		Expert #8	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Has the technology been superseded or replaced? Which of the following best describes the procedure (please choose one):	Expert #1 No. There is no functional, practical alternative for administering volatile agents in a critical care setting. The AnaConDa device represented a significantly innovative device to allow volatile agents to be delivered in a critical care setting. The AnaConDa-S is a relatively minor innovation, reducing the volume of the device and allowing it to be used in the standard configuration in the breathing circuit in much smaller patients.	
		Expert #2 It is a very novel concept in the ICU environment – traditionally we have used intravenous sedation – It has a very compact design to deliver the isoflurane but also has the scavenging system built in – which was the main reason that volatile anaesthesia is not used more in the ICU.	
		Expert #3 Blank	
		Expert #4 Novel. It translate the practice of anaesthesia into the ICU. Whilst this has always been possible using anaesthetic machines / ventilators in exceptional cases, there are significant logistic and safety concerns with this practice and as	

		such it is not widespread. AnaConDa overcomes many of the logistic issues and makes routine use of volatile sedation feasible, where appropriate.	
		Expert #5 This is a novel variation of standard care as the equipment allows the use of a novel range of sedatives within critical care (an a range that many uk intensivists have significant experience of in theatre use). The crucial question is whether there is advantage in this compared to the range of sedatives presently available	
		Expert #6 A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #7 The use of volatile anaesthetics in the management of near fatal asthma is well established. This particular method of delivery is a relatively new variation. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	

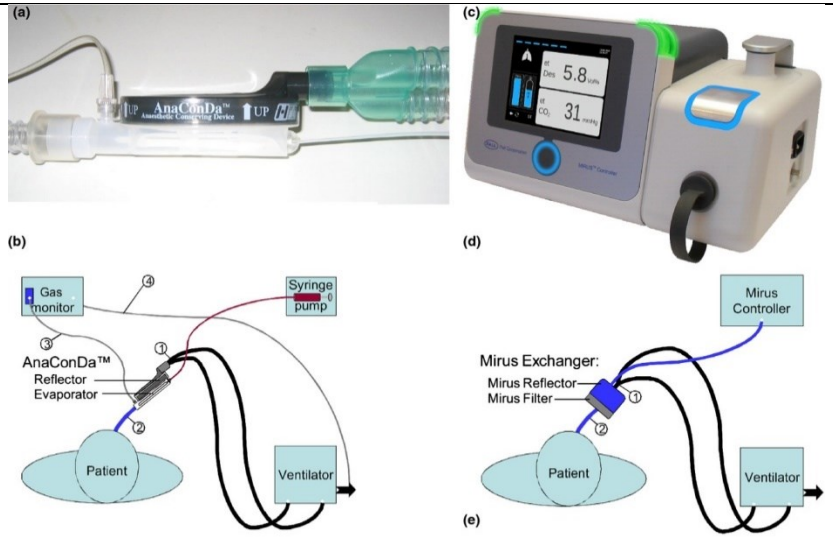
		Expert #8	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: Use of the AnaConDa would replace most intravenous and enteral sedative agents	
		Expert #2 It is an addition to standard care currently – but we are aiming to have it used routinely moving forward.	
		Expert #3 Blank	
		Expert #4 For an individual patients likely replace, but within the ICU system as a whole it would be an additional / alternative treatment option, and the potential to still use IV sedation would be retained	
		Expert #5 Replacement/ use in parallel	
		Expert #6 It has the potential to replace current standard of care, but is currently predominantly used to provide volatile sedation for those patients who	

		benefit from volatile ananesthetic gases to treat bronchospasm	
		Expert #7 It would be used in addition to the existing standard of care.	
		Expert #8	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6	

		Current sedation practice, hypnotic (propofol) plus opiate (remifentanil, Morphine, fentanyl, alfentanil) Current bronchospasm management – salbutamol, Magnesium, ketamine, etc	
		Expert #7 BTS/SIGN British Guideline on the Management of Asthma Intensive Care Society Guideline on Sedation	
		Expert #8	
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: The Mirus device is capable of delivering volatile agents in a critical care setting. It is a much more complex device than the AnaConDa (see below) which identifies end-tidal concentrations from the gas flow, injects anaesthetics during early inspiration, controls anaesthetic concentrations automatically, and can be used with desflurane, which is not possible using the AnaConDa. To my knowledge it has only been used in a very limited clinical capacity, and I am not aware of it being used in children.	

			
		Expert #2 No If we wanted to use volatile anaesthesia – we would need to use an anaesthetic machine (from the operating theatres) – however we would need to ensure we can scavenge the waste gas – we cannot do this on our ICU	
		Expert #3 Blank	
		Expert #4 No. Only alternative is to use anaesthetic machines / ventilators which have many disadvantages: lack of access in the ICU, bulk, fundamentally different mode of operation with	

		attendant risks when used by ICU staff who are not familiar (typically ICU Nursing staff will have little or no prior experience); usually lower levels of sophistication in the ventilator per se.	
		Expert #5 I have seen one other device in the past designed to provide volatile sedation in critical care, though I am not sure that this is still marketed. I am unsure if it was ever used in the UK.	
		Expert #6 Volatile gases for sedation are commonly used in anaesthetic practice to deliver anaesthesia This is done via anaesthetic machines though, which are not considered to be ideal to deliver critical care ventilation	
		Expert #7 NO	
		Expert #8	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: As above: It may be life-saving in severe acute asthma, it can be used to manage sedation in the difficult to sedate patient who may be receiving multiple intravenous and enteral sedative agents, it can be used to manage delirium and to treat withdrawal symptoms associated with intravenous agents. In addition it can provide sedation in patients with difficult or limited intravenous access & can reduce the use of intravenous fluid pumps and drugs in times of scarcity or in a pandemic.	

		Expert #2 Yes I would. Patients do appear to wake up faster – this is useful in a number of clinical scenarios including daily sedation holds that we undertake. The sedation seems much 'deeper' than with intravenous agents – so we don't need to use multiple medications to sedate some groups of patients (who traditionally may have needed 2 or 3 sedative agents)	
		Expert #3 Blank	
		Expert #4 As yet, the major patient centered benefits largely remain to be proven. Potential advantages with some level of evidence include: deep and stable sedation; faster wake up, particularly relevant after procedures (e.g. cardiac surgery); enhanced ability to make neurological assessment, especially of relevance in brain injured patients, potential improvements in lung inflammation and gas exchange in the acute respiratory distress syndrome (ARDS)	
		Expert#5 There is wide evidence that volatile gases are helpful in the management of acute exacerbations of asthma, and indeed many of us have used anaesthetic machines within critical care to deliver this. This is not a desirable approach, as the equipment is not familiar to critical care nurses and there are definite risks, however the efficacy of volatile agents as bronchodilators in this group is important and on occasion can be life-saving. In terms of sedation this is an opportunity to utilise Fet as a marker of the cerebral concentration of the sedative agent	

		which should make it easier to target appropriate sedation levels. There is some evidence (and some of our own experience supports this) that there may be some reduction in time to wake up, though whether this translates into useful alteration in time to critical care discharge is not clear. My other impression is that this may allow us to provide sedation that reduces the need for agents such as dexmedetomidate to manage post-sedation agitation. This is a very important area as the use of these agents is definitely increasing and they are a significant cost. This affect is presently anecdotal only. This also avoids some of the significant negative effects of propofol (in relation to cardiac function, propofol infusion syndrome and hyperlipidaemia).	
		Expert #6 Alternative to intravenous hypnotics for sedation, may also reduce the need for opiates. Potential quicker wake up and less delirium which may impact on length of stay	
		Expert #7 Lower dead space in comparison to an anaesthetic machine circuit Small/more compact and portable in comparison to an anaesthetic circuit Avoid side effects of IV sedation and an alternative sedation strategy in those patient groups which IV sedation may be more difficult such as acute kidney injury or liver failure.	
		Expert #8	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Severe asthmatics, those requiring multiple intravenous sedative agents, those with limited intravenous access.	
		Expert #2 Yes - the biggest patient benefit is in conditions like acute asthma – where the spasm in the airway is broken very quickly with volatile anaesthetic gases – it is used first line for these patients in our unit. Patients with renal / liver failure benefit – as there is no accumulation of the sedation in their bodies – and they wake quicker especially if being sedated for days / weeks Can be used if Propofol infusion syndrome (PRIS) is suspected or happens … Patients who have been sedated overnight (eg) drug overdoses – wake up faster and allow us to see if there are other effects of the residual drug in the system. 'Sedation holds' which we do daily are more easier to facilitate	
		Expert #3 Blank	

		Expert #4 Difficult to sedate patients' which may include but are not limited to, young patients, patients with prior history of alcohol or drug use Cardiac (or other major) surgery where post-operative ventilation occurs Brain injury ie. out of hospital cardiac arrest ARDS	
		Expert #5 Primarily asthmatics. Also the more difficult to sedate patients are definitely easier to control with this approach (eg drug or alcohol users) It may also be cost effective enough to consider its use as first line sedation. My understanding is that this is practice in some critical care units in Germany.	
		Expert #6 Bronchospasm patients, those not requiring significant opiates for pain management.	
		Expert #7 Near fatal asthma. Patients with complications of IV sedation such as those with propofol infusion syndrome.	
		Expert #8	

9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: I do not believe there is any evidence to support this, but for those requiring medium-term ventilation (5-14 days) its use MAY reduce withdrawal and delirium and hence shorten the duration of mechanical ventilation and critical care admission. A reduction in delirium and shortening the duration of mechanical ventilation and critical care admission would be associated with cost savings.	
		Expert #2 No evidence that it can improve clinical outcome – but it has the short term benefits listed above As above – mainly better treatment for some clinical conditions and possibly shorter times in ICU	
		Expert #3 Blank	
		Expert #4 Potentially improved outcomes, although in complex case of post-operative care or critical illness, there are many factors that contribute to outcome, and in my opinion the probability that	

		volatile anaesthetic sedation, as compared to IV sedation can significantly improve patient centred outcomes (length of stay, mortality) are quite low, or the size of the effect may be quite small. Potential modest improvements in process of care measures or outcomes for individual patients (ie. duration of mechanical ventilation), although it is not certain that this would be sufficient to lead to a meaningful improvement in overall productivity in an ICU. The option of volatile sedation does add resilience in the context of potential supply line shortages, as occurred with IV sedation in the Covid pandemic for example.	
		Expert #5 It is possible that this approach could make it easier for units to provide optimal sedation (by allowing measurement of Fet) and therefore improve wake up times in real life (rather in research controlled environments) Both clinical (as set out above) and financial (in reduced sedation requirements)	
		Expert #6 Possibly, in terms of reduced length of stay, ability to wean from mechanical ventilation	

		Expert #7 I am not aware of significant data to prove this as yet.	
		Expert #8	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: I think slightly less than standard care	
		Expert #2 It will cost more in the set up phase. The main costs we have incurred have been for the gas monitoring that is required for the Isoflurane level during sedation .These have to be fitted up to the existing ICU monitoring systems. We also have a mobile gas bench and monitor that can be used at any bedspace. Nurse training and trouble shooting needs to be factored in aswell After that – the daily running costs are not more.	
		Expert #3 Blank	
		Expert #4 Roughly speaking, similar or slightly higher costs with AnaConda, however, in the context of the overall cost of Critical Care, and differences	

		are small. AnaConda requires the capital purchase of gas monitoring devices approx. £5000 per unit which would otherwise not be required although these are multiple patient use. Please note the need to adjust estimated costs of propofol based on corrected dosing (see comment 2)	
		Expert #5 At worse the same and I think probably significant improvements	
		Expert #6 Dependent on availability and cost of IV sedation	
		Expert #7 There would need to be a significant amount of training for all members of the intensive care team due to the lack of familiarity in allied health professionals in using volatile anaesthetics.	
		Expert #8	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: A reduction in the use of intravenous fluid pumps and drugs in times of scarcity or in a pandemic	
		Expert #2	

		As above – the gas monitoring at the bed space is a new investment that will be needed. None of the other changes mentioned.	
		Expert #3 Blank	
		Expert #4 Limited impact. Requirement for capital expenditure on gas monitors as above. No anticpated change to staff or setting of care	
		Expert #5 As well as the drug usage as described elsewhere the AnaConda also acts as a very effective heat-moisture exchanger and this will reduce the need for heated humidifiers (a further cost saving)	
		Expert #6 Initial capital costs around the device, still require 1 syringe for the volatile, volatile costs are slowly rising	
		Expert #7 As above	
		Expert #8	
12		Expert #1:	

	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Training only; it was very simple to introduce into standard practice	
		Expert #2 Nurse training – in set up of AnaConDa / using the infusion / trouble shooting any issues with the device. Doctor training – uses / trouble shooting BME departments – addition of gas monitoring modules	
		Expert #3 Blank	
		Expert #4 AnaConDa system is 'self contained' with use of the Flurosorb system to handle the waste substance. However, an alternative, as indicated in the MIB is the use of scavenging systems (as are widely used in operating theatres were volatile anaesthetic use is ubiquitous) in the ICU. Current ICUs vary in the degree of scavenging services that are provided but if volatile sedation were to significantly increase there may be a potential impact of demand for piped scavenging in future developments. Staff training is a necessity and the support of a well written standard operating procedure.	
		Expert #5	

		Training in the use of the system has proved to be easy and adoption rapid.	
		Expert #6 none	
		Expert #7 Storage and disposal facilities of the volatile anaesthetic agents.	
		Expert #8	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	

		Expert #6 Only that associated with a new technology	
		Expert #7 Yes – this would need addressing prior to its use.	
		Expert #8	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6	

		Environmental impact of volatile use needs to be considered if used widely.	
		Expert #7 Volatile anaesthetics do have a significant environmental impact and this should be considered in comparing and contrasting to usual care. Potential for accumulation of fluoride ions with sevoflurane use resulting in kidney injury	
		Expert #8	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6 Less hypnotic use known to be associated with delirium	

		Expert #7	
		Expert #8	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: None	
		Expert #2 None to my knowledge The isoflurane is scavenged so none is released into the ICU environment	
		Expert #3 Blank	
		Expert #4 Volatiles anaesthetics are a potentially hazardous substance and are an environmental pollutant. Although the H & S risks to staff are low in routine use, measures are required to mitigate the risks associated with a significant spill. These requirements are not difficult to meet in an ICU. Volatiles can cause ‘Malignant Hyperpyrexia’ which is a potentially serious drug reaction but which is very rare.	
		Expert #5 Previous concerns related to the saturation of the device when the patient was disconnected and the syringe driver left on.	

		This is mitigated by the use of Fet monitoring which would rapidly demonstrate the high volatile concentration that this leads to.	
		Expert #6 Overall benefit in relation to sedation	
		Expert #7	
		Expert #8	
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6	
		Expert #7	

		Expert #8	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6 Most or all district general hospitals	
		Expert #7 A minority of hospitals, but at least 10 in the UK.	
		Expert #8	
19	Please list any abstracts or conference proceedings that you are aware of that	Expert #1:	

	have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	There was a recent press release from Sedana regarding the IsoConDa non-inferiority study: Sedana Medical announces positive top line result in pivotal IsoConDa study Publish date: 10 Jul 2020 06:00Regulatory Sedana Medical AB (publ) (SEDANA: FN Stockholm) today announced a positive top line result for the company's pivotal phase III study, IsoConDa. The study reached its primary endpoint; to show that IsoConDa (isoflurane), administered with AnaConDa, is an effective sedation method, for ventilator-intensive care patients, which is non-inferior to propofol. Secondary endpoints are under analysis and will be published together with the primary endpoint in a scientific journal after peer-review. The results indicate that IsoConDa is an effective and safe sedation method and will form the basis for the company's application for European market approval later this autumn. " We are proud to have conducted the world's largest study of inhaled sedation in intensive care. This is the most significant milestone in inhaled sedation since the development of the AnaConDa. The study confirms the clinical experience of IsoConDa administered with AnaConDa as an effective and safe sedation method. With the results from the study, we are in a good position for the future, both with the continued global clinical development of inhaled sedation and the work with the application for market approval in Europe," said Peter Sackey, Chief Medical Officer of Sedana Medical. “The study results are in line with the long-standing clinical experience of many doctors all over the world. Isoflurane is safe and efficacious as a sedative for invasively ventilated critically ill patients. We hope that more patients will benefit from the advantages of inhaled sedation in the future” said	

		Coordinating Investigator Germany of the IsoConDa study Assoc. Prof. Andreas Meiser, Saarland University Medical Center, Homburg, Germany. The study, which aims to support the approval of the candidate drug IsoConDa (isoflurane) for inhaled sedation in intensive care in Europe, has been conducted at 21 centers in Germany and three in Slovenia. The study is a noninferiority study, which means that its primary purpose is to show that IsoConDa, administered with AnaConDa, is non-inferior to propofol in maintaining an adequate sedation level. This is determined by comparing the proportion of time that adequate sedation depth is maintained with isoflurane compared to propofol. The study included 301 mechanically ventilated intensive care patients in need of sedation and is a so-called randomized, controlled and open-label study to confirm efficacy and safety. The patients were divided into two equal groups, where patients in one group were treated intravenously with propofol and the other with IsoConDa administered with AnaConDa. “The goal we had when we initiated the work with the IsoConDa study several years ago was to be able to register inhaled sedation with IsoConDa administered with AnaConDa and thus approach our vision to make inhaled sedation a new standard method in intensive care units around the world. With these strong results as a base, we have come a giant leap closer to our vision. We will submit our application for European market approval in 16 European countries in a first registration round as soon as possible in the fourth quarter 2020. If all goes well, we expect an approval during the second half of 2021," said Christer Ahlberg, CEO of Sedana Medical.	
		Expert #2	

		I do plan to collect data from our unit – I have not done it as of yet I would be happy to share it all with NICE	
		Expert #3 Blank	
		Expert #4 Not specifically for sedation, but as indicated above, there are some phase 2 studies demonstrating organ protective / improvments in lung biology / gas exchange in ARDS (Jabaudon, Am J Resp Crit Care Med, 2017; 195: 782-) Multiple on going trials as indicated in your appraisal. IsConDa study recently completed and awaiting publication, reportedly demonstrating non-inferiority as c.f IV sedation	
		Expert #5 n/a	
		Expert #6	
		Expert #7	
		Expert #8	
20		Expert #1	

	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.		
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: The AnaConDa could be used in almost every mechanically ventilated patient	
		Expert #2 200-300	

		Expert #3 Blank	
		Expert #4 Difficult to say. If there was a wholesale shift from IV to inhaled sedation this would be thousands or tens of thousands per year. However, assuming that use remains focused on a sub-group with specific indications, or specific potential to benefit, the numbers would be much smaller	
		Expert #5 Theoretically this could be used as the sedative of choice in critical care so could be used in most ventilated patients. Realistically there is unlikely to be that sort of uptake in changing practice.	
		Expert #6 Depends on uptake and efficacy. If equivalent to IV sedation, the number of patients equates to the number of level 3 critical care patients in the UK	
		Expert #7 Based on the document below – around 500 people are ventilated on intensive care per year due to life threatening asthma. This would seem to be the group that may benefit. https://bmjopen.bmj.com/content/bmjopen/3/9/e003420.full.pdf	
		Expert #8	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert #1: The most common problem encountered with use of the AnaConDa is the patient becoming agitated during prolonged physiotherapy when the device has to be disconnected to allow for tracheal tube suctioning. Most patients manage this disconnection well, but for those requiring unusually prolonged physiotherapy, a pre-emptive dose of intravenous sedative may be required.	
		Expert #2 Yes – if patients need to be transported (eg) CT scan / theatre – a transport ventilator that is compatible with AnaConDa is needed.	
		Expert #3 Blank	
		Expert #4 AnaConda use precludes the use of active heated humidifiers (HH) in ventilator circuits which are preferred in some ICUs, however, to the best of my knowledge the evidence of benefit for HH over HME is fairly limited and HME is considered an alternatives standard if care in some ICUs. Volatile anaesthetics require safe storage and handling and an Health and safety Risk assessment / mitigation plan (ie. spill kits etc)	

		Expert #5 No	
		Volatile agents, therefore require safe storage, but this is already done within theatre environments	
		Expert #7 Unfamiliarity with the use of volatile anaesthetics amongst staff not from an anaesthetic background or with previous anaesthetic experience.	
		Expert #8	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert #1: No	
		Expert #2 None to my knowledge	
		Expert #3 Blank	
		Expert #4 No, only that it is a novel device and therapy and as such is different from a log history of established practice	

		Expert #5 Except as above	
		Expert #6 no	
		Expert #7 NO	
		Expert #8	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Expert #1: I am confident that volatile sedation using the AnaConDa system is safe and effective with specific clinical indications. Identifying advantages over standard care would take more research; there is relatively little research into the benefits of one sedation regime over another in critical care.	
		Expert #2 Not currently	
		Expert #3 Blank	
		Expert #4	

		Studies currently in progress likely to significantly add to evidence base, one way or another. Evidence fo improvement in patient centred outcomes likely to be necessary to lead to any significant large scale move to inhaled sedation.	
		Expert #5 Blank	
		Expert #6 Possibly in relation to the incidence of delirium associated with volatile sedation vs conventional sedation	
		Expert #7 NO	
		Expert #8	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Expert#1	
		Expert#2	

	− Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#3	
		Expert #4	
		Expert #5	
		Expert #6 Beneficial outcome measures: LoS Delirium Adverse outcome measures: Same as above	

		Expert #7	
		Expert #8	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology	Expert #1: We have come to rely on the AnaConDa system since we introduced it. I have no doubt that it has improved patient outcomes particularly in severe asthma, the difficult to sedate patient and those with delirium.	
		Expert #2 I have used this technology and see it is as a very useful addition to ICU sedation . It has worked very well in specific patient groups. The nurses enjoy using it – and find it easy to set up with practice / easy to monitor and they find the patients are well sedated (no difference compaed to propofol).	
		Expert #3 Blank	

		Expert #4 Volatile anaesthetics are a useful option in the ICU and do have other applications in addition to the indication of sedation specific to this appraisal. These include effective bronchodilator therapy in refractory asthma, and potential organ protective effects. There is a learning curve to their use but our experience is that AnaConDa can be utilised safely and effectively within an appropriate governance framework.	
		Expert #5 We have found this technology easy to implement (even during the pressures of COVID) and have had buy in from all staff groups.	
		Expert #6	
		Expert #7 Amongst trainees asked about their experience with the use of this technology in hospitals they had worked, there was limited exposure. Most had experience with the use of volatile anaesthetics in the management of near fatal asthma in either a theatre setting or with the use of an anaesthetic machine in the intensive care.	
		Expert #8	