External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the sponsor's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

Title: Ambu aScope2 in unexpected difficult airways management

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Declared interests of the authors

None

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Development of the Report

Shihua Zhu worked on all aspects of the project; in particular he drafted the economic evidence review section and part of the clinical evidence review section; Fujian Song led and drafted the review on the clinical evidence review section, and provided overview on the whole report; Richard Lilford gave intelligent comments on the report and drafted the discussion section; Sue Bayliss reviewed and wrote comments on the literature search section; Peter Chilton proof-read, edited and formatted the report; Carole Cummins wrote the summary section and provided comments on the report; John Duffy provided editorial input, critique and comments; Guiqing Lily Yao led and oversaw the project, critiquing on the health economic modelling section.

Rider on 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.

Contents

1. Summary

1.1 Scope of the sponsor's submission

The population was "patients with unexpected difficult airways requiring emergency intubation including awake or anaesthetised patients with displaced tracheostomies", and "adults or children clinically evaluated for endotracheal tubes size 6 or above."

The clinical evidence came from studies of manikins or patients with anticipated (or simulated) difficult airways and from case series of patients requiring percutaneous dilatational tracheostomy.

Ambu aScope2 superseded Ambu aScope in April 2011 and study comparators were mostly "multiple-use flexible endoscopes", except in one study where the comparator was a video laryngoscope.

The outcomes measured were mainly concerned with intubation, and some device-related adverse events. Unsurprisingly, there is no direct evidence regarding serious clinical consequences, including death, hypoxic brain injury, or length of stay in Intensive Care Unit (ICU) and hospital associated with the use of Ambu aScope.

The submitted cost analysis estimated reusable flexible endoscopes costs including acquisition and maintenance. Only the costs of additional days of hospital and ICU stay were estimated, not costs of hypoxic brain injury. Many model parameters were based on exploratory assumptions with no subgroup analyses.

The Ambu aScope2 may improve equity of the availability of reusable flexible optical scopes for assisting with endotracheal intubation across settings in the NHS. According to the report there are therefore two questions to consider:

Question 1: The relative effectiveness of the Ambu aScope 2 vs. alternatives, given unfettered access to either;

Question 2: The effectiveness of procuring Ambu aScope 2 rather than reuseable equipment available for settings where unexpected difficulty may arise.

A further option (question 3) not considered by the sponsor, would be to make available a mixture of Ambu aScope2 and reusable scopes.

1.2 Summary of clinical evidence submitted by the sponsor

The clinical evidence submitted by the sponsor addressed question 1 (see 1.1 above)

Searches were made according to the NICE template and results included five randomised controlled trials (RCTs) (one reported twice) and five case series reports. Three studies were in manikins and seven in patients. Outcomes were time to intubation, intubation success rate, number of scope attempts, ease of use rating, and image quality.

In the three manikin-based RCTs, no clinically important differences in intubation time were found, but intubation success rate was lower when using Ambu aScope.

Three patient-based RCTs provided the most relevant clinical evidence, with no clinically important differences reported. Low image quality when using Ambu aScope was the main problem reported, but this had little impact on intubation. Case series of percutaneous dilatational tracheostomy (PDT) in ICUs reported general acceptability of Ambu aScope, but poorer imaging quality.

1.3 Summary critique of clinical evidence submitted by the sponsor

The search strategy conformed to the NICE template and it is likely that most relevant studies were found.

However, the EAC identified one additional RCT, which was a study still ongoing. In addition, the EAC found an abstract of a RCT (described as an ongoing study in the sponsor's submission) that compared Ambu aScope2 with a reusable fibreoptic bronchoscope in patients with simulated difficult airway.

Very few patients with unanticipated difficult airways were included in the studies, thus failing to demonstrate applicability of results to such patients. Evidence on Ambu aScope2 is lacking relative to that available for the early version, Ambu aScope. There is no direct evidence on serious clinical consequences, including death, hypoxic brain injury, or length of stay in ICU and hospital, with the use of either Ambu aScope or Ambu aScope 2.

1.4 Summary of economic evidence submitted by the sponsor

Economic evidence submitted relates to question 2 (see 1.1 above)

Database and reference list searches were made for economic evaluations. Three cost studies of the Ambu aScope and/or reusable flexible scope were found. Cost estimates were: intubation using Ambu aScope (€204, ~$266, ~£170); intubation using a reusable scope (€178, ~$232, ~£148); average cost of an intubation using a

reusable scope ($120, ~€95, ~£78); and average cost of a reusable scope for tracheal intubation per intubation in an anaesthesia department ($95, ~€75, ~£61).

In the *de novo* cost analysis, two models were used to estimate the costs and consequences associated with making Ambu aScope2 available compared with making a reusable flexible endoscope available for unexpected difficult airways requiring emergency intubation and dislodged tracheostomy. Adverse consequences were defined as those causing "more than temporary harm" in the case of dislodged tracheostomies, and as brain injury or death in the case of failed intubation. Evidence from clinical trials of Ambu aScope was not used, as this relates to question 1 only. Outcome data for failed intubation was taken from cohort studies with an unsupported assumption of a 10% risk reduction. Costs of harm were based on Hospital Episode Statistic (HES) reference costs. The cost of Ambu aScope2 was £179 per single-use scope, and the estimated mean cost of a reusable scope from NHS survey was £209 per patient/treatment.

The incremental mean cost per patient for Ambu aScope in unexpected difficult intubation in the operating theatre was £68 less than for a reusable scope; for unexpected difficult intubation in ICU it was £130 less; and for dislodged tracheostomy it was £1,556 less. The findings were sensitive to the parameter changes, but Ambu aScope remained cost-saving, except in a long lifetime or where equipment costs were substantially lower for the reusable scope.

1.5 Summary critique of economic evidence submitted by the sponsor

Appropriate searches were carried out, but could have been improved. One additional cost study was found, estimating reusable scope costs as £227. The model *compares* Ambu aScope2 with conventional reusable scopes. This implies that one or the other type of scope is going to be procured, it is a question of which. In other words Ambu aScope2 will be procured (Policy 1) or reusable scopes will be procured (Policy 2). In that case the 10% difference in effectiveness seems implausibly high (Policy 2).

The EAC believe that the sponsor should consider the scenario where Ambu aScope is used in a complementary mode to *supplement* (not supplant) reusable scopes when these are not immediately available (Policy 3). The assumption of a 10% relative risk reduction in failure/delayed rate of harm with Ambu aScope compared to

alternatives was suspect and is not supported by evidence. Nor is it plausible for policies 1 or 2.

Cost estimation for reusable scopes presents substantial difficulties and there remains great uncertainty as to the base-case cost specified. Survey response rate was low and the costs reported varied. Nevertheless, some real life NHS data were collected. Sensitivity analysis appears appropriate and the EAC confirmed the results. However, this is not of the essence – it is the issue of policy (above) that is the nub.

In summary, the submitted model does not take account of the possibility of complementary use (Policy 3), and makes an arguably implausible assumption regarding the crucial input parameter without adequate supporting evidence.

1.6 External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The clinical evidence is limited in terms of patients included, interventions evaluated, and outcomes measured (question 1). Most relevant studies are unpublished or available only as meeting abstracts. Despite relatively low image quality being reported and somewhat longer task completion time compared to reusable flexible endoscopes, Ambu aScope may be an acceptable alternative for facilitation of tracheal intubation in patients with difficult airways and for those requiring PDT, given unfettered access to one device or the other.

The *de novo* cost model (question 2) is over simplified with a crucial, and possibly implausible, assumption and wide uncertainty in sensitivity analyses. In the sponsor analysis the key potential benefit of Ambu aScope2 compared with its alternative was modelled with reference to its presumed immediate availability, but if both are purchased in equal amounts, then there is little reason to expect substantial differences in availability. It is possible that Ambu aScope2 will be more readily available because they do not need to be cleaned. It only needs to be connected to the corresponding monitor. It is possible that conventional scopes will be more available because they do not have to be re-ordered so often leading to stock-control issues. These issues are not discussed in detail and it is hard to see how either can yield such a large difference in availability as to yield a 10% difference in rates of harm when a difficult intubation is encountered. There is no real submitted evidence as to how often “supply chain” problems occur, and a switch from reusable to single-

use scopes is not the only policy option, as a single-use scope could be on hand for occasions when a reusable scope is not available (Policy 3 – see Section 1.5).

1.7 Summary of any additional work carried out by the External Assessment Centre

The EAC reviewed sponsor search strategies and expanded them. Results of non-inferiority trials were re-analysed. The EAC conducted a trial search broadening the economic evaluation search strategy. The EAC reviewed the *de novo* cost models. In appraising parameter values, a brief search of MEDLINE (Ovid) 1946 up to June week 3 2012 was made for studies reporting on the topic of delayed or failed intubation. The EAC confirmed that the results reported in the submission match the output of the submitted models. The EAC suggested that a model structure should include the scenario where Ambu aScope is used in a complementary mode to reusable alternatives. The EAC approached clinical experts for their opinions on the key clinical inputs used in the Sponsor's model.

2. Background

2.1 Overview and critique of sponsor's description of clinical context

The sponsor submission described this as a technology under assessment. *Ambu aScope2* is a single-use, sterile, disposable, flexible intubation scope that can be used to facilitate the placement of a flexible tube into the trachea to maintain an open airway. It can also be used to aid percutaneous dilatational tracheostomy (PDT), and to check the position and patency of airway devices such as endotracheal tubes and tracheostomy tubes. The design and clinical use of Ambu aScope2 is similar, or equivalent, to other flexible endoscopes, i.e. fibrescopes using fibre-optic technology, or videoscopes using video technology. The main difference between Ambu aScope2 and other flexible endoscopes is that the Ambu aScope2 is a single-use, sterile, disposable device, while conventional flexible endoscopes are reusable devices that need to be sterilised and stored appropriately.

2.1.1 Difficult airways

Flexible endoscopes are required for tracheal intubation in patients with difficult airways, which may have been caused by pregnancy, obesity, limited mouth opening, limited cervical spine movement, trauma to the face or neck, respiratory tract infections or cancers, and/or tracheostomies. According to the 'Difficult Airway Society Guidelines' (Henderson et al. 2004) the sponsor submission describes the relevant clinical pathway of unanticipated difficult tracheal intubation *during routine induction of anaesthesia* in adult patients.

2.1.2 Percutaneous dilatational tracheostomy (PDT)

The sponsor submission noted that PDT has become more popular than surgical tracheostomy in intensive care units (ICUs) as the method to open a direct airway into the trachea. The complication rate may be reduced if PDT is performed under bronchoscopic guidance. This method has been adopted in about 80% of ICUs in the UK.

2.1.3 Other issues relating to current clinical practice

In the sponsor submission, the sponsor discussed several issues relating to current clinical practice, which are summarised below.

- Inadequate training and lack of clinical experience with the technology may be a barrier to the use of fibre-optic bronchoscope (FOB) by clinicians when it

is indicated in practice: "*Cost and unavailability of suitable equipment is likely to contribute to a lack of training in the use of FOBs.*"

- Immediate availability of appropriate equipment is one of the most fundamental reasons for delayed intubation or failing to intubate a patient who requires intubation: "*Lack of essential airway equipment is a major issue, both in context of planned tracheostomies or for management of displaced tracheostomies,"* – for example in the A&E department, in ICUs, or in *"general wards where multiple use scopes are not necessarily stocked, but where emergency resuscitation is sometimes required.*"
- Serious consequences of delayed or failed intubation include death, hypoxia brain damage, and/or prolonged hospital admissions.
- One of the disadvantages of reusable scopes is the risk of cross-infection and contamination.

2.1.4 Critique of the sponsor's description of the clinical context

The sponsor submission described the clinical context. Relevant background data was mainly from published literature and the '*4th National Audit Project of The Royal College of Anaesthetists and the Difficult Airway Society*' (Royal College of Anaesthetists 2011). The sponsor submission emphasised the inadequate availability of equipment in difficult airway management, particularly in settings where reusable flexible scopes are not routinely stocked, and where emergency resuscitation is sometimes required. The sponsor argues that the lack of flexible scopes may have contributed to delayed or failed intubation. Part of the sponsor argument is that the risk that a flexible scope will not be available when needed will be reduced under a policy to deploy single-use, rather than reusable, devices across an institution. This may have some face validity since a scenario can be envisaged where a reusable device is not available as it has been sent away for sterilisation. However, the size of this problem is not described and no evidence is presented to show that single-use devices reduce the size of the problem – indeed collating such evidence would be tricky (see below). Nor does the sponsor countenance the opposite problem – that a single-use device might not be available because it has been disposed of and not resupplied.

Clinical experts confirmed that availability of scopes could be problematic, but it was difficult to estimate how often this occurred, being dependant on context. In a study of ward tracheostomy safety, a search of the National Patient Safety Agency (NPSA) database for the period 1st October 2005 to 30th September 2007 for the free text

term “scope” found eight reported incidents, which represented complete data for the period, with an estimated one in ten incidents having been reported (personal communication with a clinical expert 20th July 2012). Four of these incidents were reported as having resulted in temporary harm and an increased length of stay; one in temporary harm; and three in no harm. In some cases improving information provided to staff and improving communication about storage and availability of emergency equipment could have mitigated the risks involved without increasing scope availability.

Clinical experts considered that there were some differences between Ambu aScope2 and reusable scopes, which were mainly unimportant if the choice was between delayed use of a reusable fibrescope and immediate use of an easily accessible single-use scope. Due to the insertion cord diameter the Ambu aScope, cannot be used with some other intubation devices. For example, clinical experts pointed out that it cannot be used with the Aintree catheter, a relatively low-skill intubation device.

2.2 Overview of sponsor’s description of ongoing studies

The sponsor has searched for ongoing trials, but has failed to clarify where these searches were conducted. (Later on in the submission document, Section 7.1.2, they state that they have searched ClinicalTrials.gov and Cochrane CENTRAL for ongoing trials). They pinpointed two studies likely to become available in the next 12 months that were currently recruiting patients.

- ClinicalTrials.gov identifier: NCT01467739. *Evaluation of the Ambu ® aScope® for Tracheal Intubation in Difficult Airways.* A randomised, open-label study to evaluate Ambu aScope versus a conventional reusable fiberscope for tracheal intubation in difficult airways due to cervical immobilization by a cervical collar.
- ClinicalTrials.gov identifier: NC01215695. *Video-laryngoscope With a Novel Video-stylet for Difficult Intubation.* A randomised study to compare Ambu aScope and a pre-formed stylet for tracheal intubation in patients with predicted difficult airway or an immobilised cervical spine.

The two trials have NCT pre-fixed trial identifiers, suggesting that ClinicalTrials.gov was searched. It would be helpful if the sponsor had stated this, together with the date searches were carried out. The completion dates for both these trials have passed, but the EAC searched ClinicalTrials.gov for clarification and both have yet to

be denoted as completed. The sponsor notes that parts of NCT01215695 have been published in the form of a poster presentation (Lenhardt et al. 2011).

The sponsor is also aware of a further ongoing study (Hagberg, University of Texas), which is detailed in Section 5.1 and which compares performance of optical intubation with blind intubation (this is now listed in ClinicalTrials.gov, identifier NCT011656967). However, this study does not seem relevant to the decision problem.

Searching additional sources for ongoing trials beyond those listed in Section 7.1.2 would have been beneficial here. The EAC conducted its own searches of ClinicalTrials.gov, ISCTRN database and WHO ICTRP and located the following additional trial which has not been mentioned by the sponsor – ACTRN1261101235998, available at: http://www.anzctr.org.au/ACTRN12611001235998.aspx. This is being sponsored by the Department of Anaesthesia and Pain Management, Royal Melbourne Hospital and Ambu A/S and compares Ambu aScope with the Karl Storz intubating bronchoscope. The trial was registered 2nd December 2011, so it is unlikely to release any results in the next 12 months and for this reason it has not been included.

During searches of the European Society of Anaesthesiologists meeting abstracts the EAC also identified an abstract in which the results of trial NCT01467739 were presented (Schoettker et al. 2012). Therefore, there would appear to be some results available for both of the two ongoing trials identified by the sponsor, together with an additional study that they did not identify. Note that clinical trials are relevant to only a part of the decision problem – is the re-use of a device as, or more, effective than reusable devices in facilitating intubation (or tracheal dilation). Issues relating to the supply chain (discussed above) would require different (and arguably less conclusive) types of study.

2.3 Critique of sponsor's definition of the decision problem

2.3.1 Population

The relevant population described in the final scope by NICE is "patients with unexpected difficult airways requiring emergency intubation including awake or anaesthetised patients with displaced tracheostomies", and that Ambu aScope2 "can be used in adults or children who have been clinically evaluated for endotracheal tubes size 6 or above."

However, the clinical evidence provided in the sponsor submission was obtained from either studies of manikins or of patients with anticipated difficult airways (see Section 3 for details). The extent to which evidence from manikin-based studies is relevant to real patients with difficult airways is unclear. Of the other studies, the most relevant and valid evidence were from three patient-based randomised controlled trials (RCTs). However, two of the three RCTs included patients with anticipated difficult airways (Kristensen 2011; Lenhardt et al. 2011), and one included patients with simulated difficult airways (immobilised neck with semi-rigid cervical collar) (Schoettker et al. 2012). Two studies of case series included patients requiring PDT in ICUs (total N=20) (Jamadarkhana et al. 2011; Perbet et al. 2011). None of the available controlled trials included patients with unanticipated difficult airways, and no studies were explicitly conducted in Accident and Emergency (A&E) departments. Therefore, it is uncertain whether the results of the included studies could be applied to "patients with unexpected difficult airways requiring emergency intubation including awake or anaesthetized patients with displaced tracheostomies", as specified in the final scope.

2.3.2 Intervention

The specified intervention in the final scope is "Ambu aScope2". The Sponsor provided details on regulatory information in the submission, including instructions for use; CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity; and quality systems (ISO 13485) certificate. The sponsor has satisfied the regulatory requirements in the submission with the relevant documents. In addition, the sponsor stated that:

- In October 2010, "aScope 2 was reclassified and approved as a Class IIa medical device following technical file review by BSI, in order to include visual guidance during PDT as part of its indications for use."
- "Ambu aScope2 superseded 'aScope' in April 2011. It is the same product and is covered by the same CE Mark, with a number of enhancements that include the easy clearing membrane, the oxygen adapter and the removal of the 30-minute timeout feature."

2.3.3 Comparator(s)

The final scope by NICE specified the comparators as "multiple-use flexible endoscopes (fibrescopes using fibre-optic technology or video scopes using video technology)". In the controlled trials obtained, the comparators used were reusable flexible optical scopes that are commonly used in the UK (manufactured by Storz,

Pentax or Olympus). However, in one of the studies included in the submission (Lenhardt et al. 2011) Ambu aScope was combined with a GlideScope video laryngoscope (GVL), and compared with a combination of GVL and a pre-formed rigid stylet. In effect, the Ambu aScope was compared to a rigid stylet, which is not the relevant comparison as set out in advance. Thus, only two RCTs are relevant (Kristensen 2011; Schoettker et al. 2012). The real problem is that there are two questions in play:

Question 1: Given unfettered access to each type of device, which is the most effective?

Question 2: Assuming that there is no material differences in devices under question 1, then which policy is most cost-effective – Policy 1, order single-use device; or Policy 2, order reusable devices (see Section 1.5). Later the EAC will suggest a third policy.

2.3.4 Outcomes

The relevant outcomes described in the final scope include:

- Incidence of delayed or failed intubation.
- Clinical consequences associated with (difference in) delayed or failed intubation (including death, hypoxic brain injury, and length of stay in ICU and hospital).
- Incidence of successful intubation [reciprocal of fist point].
- Device-related adverse events.

The outcomes measured in the included studies were mainly the success rate of intubation, time to intubation, ease of use, and image quality. These outcomes are relevant to the outcomes specified in the final scope. However, there is no direct evidence regarding serious clinical consequences, including death, hypoxic brain injury, or length of stay in ICU and hospital, associated with the use of Ambu aScope. None of the included studies were primarily designed to evaluate safety and adverse events. Note, however, that the 'clinical consequences' are all extremely rare and, from a statistical and clinical trial design perspective, it is unrealistic to think that differences in these end-points could be detected in a clinical trial. Note, however, that all this relates directly to question 1 and only indirectly to question 2.

2.3.5 Cost analysis

The cost analysis in the sponsor submission considered all relevant issues specified in the final scope by NICE. From a National Health Service (NHS) perspective the sponsor estimated costs of reusable flexible endoscopes, including acquisition and maintenance-related costs.

The final scope by NICE required the consideration of "the costs attached to acute recovery, clinical management, rehabilitation and long-term care of those with hypoxic brain injury". In the sponsor submission the costs of additional days of hospital and ICU stay due to delayed/failed intubation were estimated. The sponsor also mentioned two possible savings that have not been possible to quantify – savings due to reduced risk of cross-contamination and infection; and reduced litigation for NHS Trusts following deaths and brain injury related to delayed/failed intubation. The question in play here is really question 2.

Because of a lack of data, many model parameters used in the submission were based on 'exploratory assumptions'. A wide range of sensitivity analyses were conducted in the sponsor submission.

The argument is not advanced that intubation will be more successful with a single-use device, rather that a single-use device can be more readily accessed for use in an unexpected situation compared to a multi-use device (although this is conjectural as RCTs were *not* designed to investigate this point). One problem is that the forms that the sponsor and the EAC are required to complete do not easily accommodate this assessment, which is partly a standard issue of effectiveness (question 1), but mostly a service delivery/ supply-chain issue (question 2).

2.3.6 Subgroups

No subgroup analyses were explicitly specified in the final scope by NICE.

2.3.7 Special considerations, including issues related to equality

The final scope by NICE outlined that people at greater risk of airway complications are those with conditions affecting cervical spine mobility, which may include: pregnant women, people who are obese, people in whom trauma to the face or neck has occurred, and people with respiratory tract infections or cancers. Other groups covered by the Equality Act (2010) are patients with rheumatoid arthritis and limited spine movements, and longer term tracheostomy patients.

The Ambu aScope2 may improved equity of access to optical scopes for endotracheal intubation across different settings in the NHS. The EAC team has not noted any other equality issues.

3. Clinical evidence

3.1 Critique of the sponsor's search strategy

(Please note this is relevant to question 1.)

3.1.1 Identification of studies

3.1.1.1 Published studies

The search strategy was compiled based on principles of the CRD (presumably via their guide: Centre for Reviews and Dissemination. CRD guidance for undertaking reviews in health care. York: CRD; 2009. http://www.york.ac.uk/inst/crd/index_guidance.htm). The range of resources the sponsor searched includes databases, conference abstracts, sponsor's databases and ongoing trials sources.

The sponsor lists the databases searched as the Cochrane Library, MEDLINE, MEDLINE In Process (Ovid) and EMBASE (Ovid). The search details are well documented including platforms via which databases are to be searched, date ranges within the databases searched, and the date the searches were run.

The sponsor describes the strategy itself as comprising clinical keywords (presumably by this they mean free text as the strategy detailed in the appendix includes no controlled index terms). The decision not to use index terms such as MeSH Medical subject headings is not explained. For comments on the composition of the strategy itself, see comments on appendix 1.

The date limit is given as 1992 onwards, although no rationale for this is given.

The sponsor has chosen to keep the strategy sensitive by not using language or publication type limits, which, as they suggest, will keep the search as broad as possible.

A further method the sponsor has used is to search the reference lists of relevant study publications, which again adds to the sensitivity of the search.

A flow diagram (Figure 3) illustrates the numbers of published studies identified through database searching. Database searches alone identified 38 studies initially. Fourteen studies were identified through other sources, although no further detail is given. Of the total of 52, 38 remained after removal of duplicates for screening. Ultimately 13 were included in the quantitative synthesis.

3.1.1.2 Unpublished Studies

Unpublished data were sought extensively from the following sources: the sponsor, authors of relevant studies, ongoing trials registers (including contacting key investigators of studies) and the Sponsor and User Facility Device Experience (MAUDE) database of adverse events via the US Food and Drug Administration (FDA). In Section 7.7.3 the sponsor reported that no adverse events associated with Ambu aScope were listed on the MAUDE database.

Grey literature searches were carried out by searching the European Society of Anaesthesia (ESA), and European Society of Intensive Care Medicine (ESICM), both covering the period 2006-2012, as well as the websites of the European Society of Anaesthesiologists (ESA) (2006-2012), and the Society for Technology in Anaesthesia (STA) (2011-2012). Searches by the EAC identified an additional item (Schoettker et al. 2012) via the ESA annual meetings online; the abstract of which was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence.

The sponsor notes having attempted to obtain abstracts from past meetings of the Difficult Airway Society and the Society of Airway Management, neither of whom responded in time.

The abstract databases above were searched using a combination of free text and subject headings.

3.1.2 Commentary on information provided in Section 10.1 Appendix 1: Search strategy for clinical evidence (Section 7.1.1)

The search strategy is explicitly described, as required by the NICE template. The databases searched (MEDLINE, MEDLINE In Process, EMBASE and the Cochrane Library) are listed along with the span of dates covered and the platform via which the database was accessed. However, the sponsor did not provide the individual search strategies for MEDLINE, EMBASE, MEDLINE In Process, and Cochrane's CENTRAL in the appendix – instead there is only a combined strategy for MEDLINE and EMBASE.

Searches were run on 2nd May 2012 and were limited to the period 1992 onwards. The rationale for this is not made clear, although it may relate to the technology. A search strategy is provided (Table 58), although this appears to be designed to be run across MEDLINE and EMBASE together. Ideally the strategies for each database search should be provided in the appendices.

The strategy combines terms for the indication and the technology using the Boolean "AND" operator. The sponsor does not use any index terms such as MeSH, when ideally a strategy should contain a mixture of text words and subject index headings. However, the terms chosen are appropriate and truncation has been employed to capture a range of word endings and thus broaden the search. The term "fibre*" is used where "fiber*" should ideally also be used to pick up references to "fiberscope" or "fiberoptical tracheal intubation". This may have resulted in studies being missed.

Overall, however, it is likely that the strategy will have located most relevant studies, especially given the other supplementary methods employed (reference searching, contacting experts, searching trials registers etc).

As previously stated, the sponsor should also have provided the complete search strategies used for the Cochrane Library and MEDLINE In Process. It is not clear whether the search strategy given is designed to be run across MEDLINE In Process as well. For the above reasons it is not possible to re-run the strategies provided with any certainty in order to compare the results with those given by the sponsor.

3.1.3 Commentary on Section 10.1.5 of Appendix 1 Additional searches

Abstracts were sought from the American Society of Anaesthesiology (this should read the American Society of Anesthesiologists) and the European Society of Intensive Care Medicine for the period 2006-2012.

The websites of the European Society of Anaesthesia (this should read the European Society of Anaesthesiologists) and the Society for Technology in Anaesthesia (Anesthesia) were searched for the periods 2006-2012 and 2011-2012 respectively. The terms used to conduct these searches are provided and appear appropriate.

It is not reported here how many references were located by these means, although presumably any found will have been incorporated into the flow chart (fig 3) under "additional records identified through other sources".

Direct contact was made with the Difficult Airway Society and the Society of Airway Management in order to access their past meetings abstracts, but no timely response was obtained.

As noted previously in "*Section A: Overview of sponsor's description of ongoing studies*", the sponsor reported having searched ClinicalTrials.gov for ongoing and completed trials. This search should ideally have been supplemented by searching additional clinical trials registers, such as ClinicalTrials MetaRegister and WHO International Clinical Trials Registry Platform http://www.who.int/ictrp/en/.

The EAC searched these supplementary sources and in doing so located an additional trial in ClinicalTrials.gov, ISCTRN database and WHO ICTRP, and located the following additional trial which has not been mentioned by the sponsor ACTRN1261101235998, available at http://www.anzctr.org.au/ACTRN12611001235998.aspx

During searches of the ESA meeting abstracts the EAC also identified an abstract in which the results of trial NCT01467739 were presented (Schoettker et al. 2012). The abstract of this was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence. Therefore, there would appear to be some results available for all of the ongoing trials identified by the sponsor.

3.2 Critique of the sponsor's study selection

Detailed selection criteria used for published and unpublished studies were provided in the sponsor submission. The inclusion and exclusion criteria used in the sponsor submission are appropriate, according to the decision problems specified in the final assessment scope.

Patients included were adults or children with expected or unexpected difficult airway, or in PDT. Manikins included were configured to simulate difficult airway. Studies included were published journal papers and congress abstracts from 1992 to 2012 and 2007 to 2012, respectively. The included outcomes were intubation success or failure rate and intubation time, though some also included other outcome measures, for example, time to scope position, length of hospital stay, rate of contamination and cross-infection, and device related relevant adverse events.

The exclusion criteria used for the selection of studies were reasonable. Patients or manikins with normal airways were excluded (Charles et al. 2011; Galindo-Menendez & López-Garcia 2010; Kristiansen 2011; Laursen et al. 2011; Missaghi et al. 2010). Outcomes irrelevant to efficacy, or safety were excluded (Seramondi et al. 2010).

The same inclusion and exclusion criteria were applied to identify both published and unpublished studies. The sponsor included a total of nine published studies and one unpublished study in their submission.

3.3 Included and excluded studies

The sponsor submission identified 20 possibly relevant studies (19 published (Table 6 of the submission) and one unpublished (Table 7 of the submission)). Of these, six RCTs and five case series reports were included in the sponsor submission, and six studies were completely excluded. The other four studies were not included in the

submission, but data were available from the submission's appendices of supplementary information. See below for details on the included and excluded studies.

3.3.1 Included studies in the sponsor submission

The sponsor submission included six RCTs (Kristensen 2011; Kumar et al. 2011; Lenhardt et al. 2011; Piepho et al. 2010; Scutt et al. 2011; Vijayakumar et al. 2011) and five studies of case series (Jamadarkhana et al. 2011; Perbet et al. 2011; Piepho et al. 2010; Pujol et al. 2010; Vincent et al. 2011). Of the included studies, one paper reported results from two studies (a manikin-based RCT, and a case series of five patients with difficult airways) (Piepho et al. 2010). In addition, one study by Lenhardt et al., had references identifying a meeting abstract (Lenhardt et al. 2011) and the study protocol (Lenhardt et al. 2010; ClinicalTrials.gov identifier: NCT0121569). After examining all the included studies, we found that one RCT was mistakenly counted twice in the sponsor submission. Both Vijayakumar et al. (2011) and Kumar et al. (2011) reported results from the same study. Therefore, there are five independent RCTs and five reports of case series in total (Table 3.1).

Of the ten included studies, five were formally published as journal articles (Piepho et al. 2010; Pujol et al. 2010; Scutt et al. 2011; Vijayakumar et al. 2011), four only reported results in conference abstracts (Jamadarkhana et al. 2011; Lenhardt et al. 2011; Perbet et al. 2011; Vincent et al. 2011), and one study had an unpublished full report available (Kristensen 2011).

Three of the ten included studies evaluated the performance of Ambu aScope in manikins (Piepho et al. 2010; Scutt et al. 2011; Vijayakumar et al. 2011), while seven studies evaluated Ambu aScope in patients with difficult airways (Jamadarkhana et al. 2011; Kristensen 2011; Lenhardt et al. 2011; Perbet et al. 2011; Piepho et al. 2010; Pujol et al. 2010; Vincent et al. 2011). Since results of studies of patients with difficult airways are more relevant to clinical practice (though findings from manikin-based studies may also be useful), we separated the manikin-based studies and patient-based studies more explicitly in Table 3.1.

Furthermore, the sponsor submission mentioned three ongoing studies that were relevant (ClinicalTrials.gov Identifier: NCT01467739, ClinicalTrials.gov Identifier: NCT01215695, and ClinicalTrials.gov Identifier: NCT011656967 [now registered]). Results from two of these were reported in abstracts, one of which was included in the sponsor submission (Lenhardt et al. 2011), and one of which was subsequently

provided by the sponsor (as the presentation had been made after the initial submission of evidence) (Schoettker et al. 2012).

Table 3.1. Main characteristics of studies included in the sponsor submission.

Study	Design	Setting (country)	Intervention	Subjects	Sponsor
Manikin-based studies					
Piepho et al. 2010. Journal article	RCT	SimMan manikin (Laerdal) (Germany)	Ambu aScope vs. Storz flexible intubation fibrescope	N=21: Anaesthetists with experience in fibre-optic intubation (at least 50) The manikin: (1) a normal airway, (2) an airway with decreased cervical range of movement and pharyngeal oedema.	Equipment provided by Ambu
Scutt et al. 2011. Journal article	RCT	3 manikins: Airway Trainer (Laerdal); Bill 1 (VBM); AirSim (Trucorp Ltd) (UK)	Ambu aScope vs. Pentax F1 13RBS; with or without a SAD (supraglottic airway device)	N=22: Volunteer anaesthetists who were familiar with, or skilled in, fibre-optic intubation (previous experiences: 0-30) Note: manikins were not explicitly modified to simulate difficult airways.	Equipment provided by Ambu
Vijayakumar et al. 2011. *Kumar et al. 2011.* Journal article	RCT	AirSim Multi (Trucorp Ltd) (UK)	Ambu aScope vs. Olympus reusable fibreoptic scope	N=75: Anaesthetists with at least 10 previous fibrescope placements The manikin was modified by narrowing the airway in 3 places along the path of the scope.	Equipment provided by Ambu
Patient-based studies					
Kristensen. 2011. (R-PS-7-2009) Unpublished report AIC	RCT	OR (Denmark)	[redacted]	[redacted]	[redacted]

Lenhardt et al. 2011. NCT01215695 Abstract	RCT	Unclear (USA)	GVL + Ambu aScope vs. GVL + Pre-formed stylet (GlideScope)	N=140 Patients with anticipated difficult airways. ASA physical status 1–3.	University of Louisville
Jamadarkhana et al. 2011. Abstract	Case series	General and Neurosurgical ICUs (UK)	**Ambu aScope2**	N=10 Adult patients who underwent PDT. In 9 patients PDT was performed between 3 and 6 days after tracheal intubation.	Technical support from Ambu
Perbet et al. 2011. Abstract	Case series	ICU (France)	Ambu aScope	N=10 Long-term ventilated patients requiring a bedside PDT. IGS II 46 (39-62)	N/A
Piepho et al. 2010. Journal article	Case series	Unclear (Germany)	Ambu aScope	N=5 Three awake adult patients with predicted difficult airway, and 2 patients with unanticipated difficult airways. 2 oral and 3 nasal.	Equipment provided by Ambu
Pujol et al. 2010. Journal article	Case series	Unclear (Spain)	Ambu aScope	N=10 Adult patients with predicted difficult airways. Arne score median 21.5 (range 11– 41).	Equipment provided by Ambu
Vincent et al. 2011. Abstract	Case series	Unclear (UK)	**Ambu aScope2**	N=8 Awake adult patients for elective ENT and maxillofacial surgeries with anticipated difficult airways.	Technical supported by Ambu
Ongoing studies					
ClinicalTrials. gov Identifier: *NCT01467739* Same study as: Schoettker et al. 2012. Abstract Ongoing *	RCT	Unclear (Switzerland)	Ambu aScope2 vs. fibreoptic bronchscope	N=100 Patients with **simulated** difficult airway. After induction of general anaesthesia, the neck was immobilised with an appropriately sized semi-rigid cervical collar.	FLAVA foundation
ClinicalTrials. gov Identifier: *NCT01215695*	RCT	Unclear (USA)	Ambu aScope vs. Preformed stylet	N=140 Patients with anticipated difficult	University of Louisville

Same study as: Lenhardt et al. 2011. Abstract Ongoing			(GlideScope)	airways. ASA physical status 1–3.	
Hagberg. Ongoing	RCT	Unclear (USA)	Optical intubation using aScop vs. blind intubation using disposable Fastrach	N=66 Patients with normal airway.	Equipment partly provided by Ambu
Extra studies identified by EAC					
ACTRN1261100123599 8 Ongoing	RCT	Unclear (Australia)	Ambu aScope vs standard fibreoptic endoscopy	N=70 Adult patients undergoing general anaesthesia, asleep orotracheal intubation. ASA I-III.	Equipment provided by Ambu

ASA: American Society of Anesthesiologists physical status; ENT: Ear, Nose and Throat; GVL: GlideScope video laryngoscope; PDT: percutaneous dilatational tracheostomy; SAD: Supraglottic Airway Device.

* This abstract was identified by the EAC, and was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence.

In addition to the studies described in Table 3.1, the sponsor submission included four studies that were relevant to the scope and provided “additional supplementary information” (Austin et al. 2011; Gernoth & Genzwuerke 2010; Kristensen et al. 2010; Samuande et al. 2010). The main characteristics of the four studies are presented in Table 3.2.

Table 3.2. Characteristics of studies that provided supplementary evidence

Study	Design	Setting (country)	Intervention	Subjects	Sponsor
Austin et al. 2011. Abstract	Unclear	ICU (UK)	Ambu aScope vs. standard fibreoptic equipment	N=5 (Ambu aScope used) Patients requiring a bedside PDT in ICU	Unclear
Gernoth & Genzwuerke. 2010. Abstract	Case series	ICU (Germany)	Ambu aScope	N=4 Long-term ventilated patients in ICU who required PDT	Unclear
Kristensen et al. 2010. Abstract	Case series	Unclear (Denmark)	Ambu aScope	N=5 Patients with difficult airways	Unclear
Saumande et al. 2010. Abstract	RCT	Manikin: (KarlStorz) (France)	Ambu aScope vs. Ambu aScope + Pentax Airwayscope (AWS)	N=10: Anaesthetists previously performed <20 fibreoscopies and <5 AWS. Difficult airway mannequin	No funding received for this study

AWS: Airwayscope; ICU: Intensive Care Unit; PDT: percutaneous dilatational tracheostomy;

3.3.2 Studies excluded from the submission

The sponsor submission excluded six identified studies for various reasons:

- Irrelevant patients: Ambu aScope used in patients with normal airways (Laursen et al. 2011; Missaghi et al. 2010); or used in manikins with normal airways (Galindo-Menédez & López-Garcia 2010).
- Irrelevant decision problems: control of distal bronchial structures (Charles et al. 2011); or checking the position of double lumen tubes (Seramondi et al. 2010).

The report was written by a specialist at Ambu (Kristiansen 2011), and therefore it was excluded from the submission.

3.3.3 Relevant studies identified by the EAC team

We identified an abstract [4] that reported results from one of the ongoing studies included in the sponsor submission (Schoettker et al. 2012). This was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence. This RCT compared Ambu aScope2 and reusable fibre-optic bronchoscope in 100 patients with simulated difficult airway (Table 3.1).

We also identified a relevant ongoing RCT conducted in Australia (ACTRNI 2611001235889). In this ongoing study, Ambu aScope will be compared with a standard fibre-optic endoscopy for orotracheal intubation in adult patients undergoing general anaesthesia (Table 3.1). This ongoing trial was identified by searching WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), which covered international multiple trail registries. The sponsor submission searched only ClinicalTrials.gov, which was clearly inadequate.

3.3.4 Studies excluded by the EAC team

Both Vijayakumar et al. (2011) and Kumar et al. (2011) reported results from the same study – we excluded Kumar et al. (2011) as this was an abstract with limited details.

As requested by the EAC team, the sponsor checked the possible duplicate publications of the same data in the identified studies. It was found that two supplementary studies shared data from one study (Austin et al. 2011; Gernoth & Genzwuerke 2010).

3.4 Overview of methodologies of all included studies

Details on the methodology of each of the included studies are provided in Tables 8 to 18 in the sponsor submission. The sponsor submission included three manikin-based studies and seven patient-based studies. In addition, the EAC provided some corresponding assessment of one RCT identified by the EAC, which was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence. (Schoettker et al 2012).

The three manikin-based studies were all RCTs in which the study participants were volunteer anaesthetists who performed intubations using Ambu aScope and a control device, with the order of device use being randomised. In addition, the authors randomised the order of simulated manikin scenarios in two of the studies (Piepho et

al. 2010; Scutt et al. 2011; Vijayakumar et al. 2011), and the order of route in one study (Scutt et al. 2011).

Of the eight patient-based studies (including one RCT identified by the EAC), three were RCTs and five were case series reports. In one of the three RCTs (Lenhardt et al. 2011), randomisation was stratified according to whether the patients had a predicted difficult airway or an immobilised cervical spine. In the Kristensen 2011 RCT, patients were randomised by sequentially drawing envelopes. The randomisation method used in the Schoettker et al. (2012) RCT was unclear.

Outcomes measured in the included studies predominantly included time to intubation, intubation success rate, number of scope attempts, ease of use rating, and image quality (Table 3.3). The included studies were not primarily designed (powered) to evaluate safety or adverse effects outcomes (as stated above, these events are very rare).

Standard statistical tests were conducted in the three manikin-based and three patient-based RCTs. However, statistical tests were not conducted in the five studies of case series, possibly because of the extremely small number of cases (≤10) included in these studies.

One manikin-based RCT (Vijayakumar et al. 2011) and two patient-based RCTs (Kristensen 2011; Lenhardt et al. 2010) were explicitly designed as ***non-inferiority studies***. For non-inferiority studies it is necessary to decide the minimally important clinical difference in results between Ambu aScope and the control device. This was estimated to be 30 seconds in the manikin-based RCT, (Vijayakumar et al. 2011) ten seconds in the study by Lenhardt et al. (2010) and [redacted] in the study by Kristensen (2011).

Table 3.3. Outcomes measured in the included studies

Study	Design	Outcomes measured	Notes
Piepho et al. 2010.	RCT	- Time required to position the scope (between touching the handle of the scope and passage of its tip through the glottis). - Time for successful tracheal intubation. - Rating of the devices, including the picture quality, rigidity, and tip articulation.	Statistical tests conducted
Scutt et al. 2011.	RCT	- Time to intubation (from starting endoscopy with a preloaded tracheal tube to first lung ventilation).	Statistical tests conducted

		- Number of attempts. - Participant-reported problems. - Overall usefulness rating. - Rating of device quality and image quality.	
Vijayakumar et al. 2011.	RCT	- Time to task completion (from picking up the fibrescope to the tip of the fibrescope appeared through the manikin's left main bronchus). - Number of tip surface collisions. - Participants' impression on the ease of use.	The margin of equivalence: a difference in time to task completion of at least 30 seconds.
Kristensen. 2011.	RCT	- [redacted]	[redacted]
Lenhardt et al. 2010.	RCT	- Time to intubation (defined as the time between inserting scope for visualisation of the epiglottis until successful intubation with proof of end-tidal CO_2). - [redacted]	[redacted]
Jamadarkhana et al. 2011.	Case series	- Ease of use. - Quality of image. - Arterial blood gases, ventilator and cardiovascular parameters.	Statistical tests not performed
Perbet et al. 2011.	Case series	- Rating of conditions of procedure (duration, visualisation).	Statistical tests not performed
Piepho et al. 2010.	Case series	- Not specified, reported experience of using Ambu aScope in five cases.	Statistical tests not performed
Pujol et al. 2010.	Case series	- Intubation success. - Ease of use. - Image quality.	Statistical tests not performed
Vincent et al. 2011.	Case series	- Intubation success. - Time for scope position. - VRS: performance of Ambu aScope2.	Statistical tests not performed
Schoettker et al. 2012. *NCT01467739*	RCT	- Time to reach the carina. - Time to obtain an end tidal CO_2 curve.	Statistical tests conducted
Hagberg *Ongoing*	RCT		

VRS: verbal rating scores.

3.5 Overview and critique of the sponsor's critical appraisal for each study

3.5.1 Differences in methodology between the included studies

In the sponsor submission, the sponsor described differences across the included studies in terms of devices evaluated, comparators, study participants, baseline characteristics, and clinical settings (Table 3.4). The description of the differences across studies was generally clear and appropriate. The EAC team provided some comments or supplementary information in Table 3.4. A few important issues are summarised below:

- Ambu aScope evaluation: The sponsor identified only two small case series reports that evaluated Ambu aScope2 (Kumar et al. 2011; Vijayakumar et al. 2011). The abstract of a third study was provided by the sponsor after the initial submission of evidence that looked at 100 patients with simulated difficult airways (Schoettker et al. 2012). In the study by Lenhardt et al. (2011), Ambu aScope was combined with the use of GVL, as described above. In part of the manikin-based study by Scutt et al. (2011) three supraglottic airway devices (SAD) were also used.
- Comparators: A range of comparator reusable scopes were used in the controlled studies: Olympus, Storz and Pentax. The comparator in the Lenhardt et al. (2011) study was a pre-formed stylet provided by the sponsor of the GVL (Verathon Medical, Bothell, WA) (Lenhardt et al. 2010), and does not seem relevant to the scope of the report.
- Study participants: Studies included patients with expected difficult airways or patients requiring PDT. One RCT (Schoettker et al. 2012) included patients with simulated difficult airway (Table 3.1). As stated before, the available studies included very few patients with unanticipated difficult airways.
- Settings: Clinical settings were unclear in many included studies. There were no studies that explicitly included patients in A&E departments.

Table 3.4. Summary of differences between the included studies

Items	Description in the submission	EAC commentary
Ambu aScope	Ambu aScope was evaluated in eight of the ten included studies. Only two small case series reports evaluated Ambu aScope2.[6,14]	Ambu aScope2 was also evaluated in Schoettker et al. (an EAC identified abstract) (Schoettker et al. 2012).
Patient populations	A variety of manikins used. Patient-based studies included patients with expected difficult airways; patients with simulated difficult airways; or patients requiring PDT.	The available studies included very few patients with ***unanticipated*** difficult airways
Baseline differences	Manikin-based studies included volunteer anaesthetists who had different previous experience of endotracheal intubation Patient-based studies included patients with diverse clinical characteristics, with different causes and severity of difficult airways.	In RCTs, patient baseline characteristics are comparable between study arms, as a consequence of randomisation.
Delivery of intervention	Nasal and oral	In Lenhardt et al. (2011), Ambu aScope was combined with the use of GVL (the GlideScope Video laryngoscope)
Care setting	Patient-based studies: two included studies [6,7] and two supplementary studies [15,16] involving ICU patients requiring PDT. Other studies included patients in other settings (for example, operating rooms)	Clinical settings were unclear in many included studies. There were no studies explicitly in A&E department
Comparators	A range of comparator scopes in the controlled studies: Olympus, Storz and Pentax	The comparator in the Lenhardt et al. (2011) study was a pre-formed stylet provided by the sponsor of the GVL (Verathon Medical, Bothell, WA) (Lenhardt et al. 2010).

3.5.2 Critical appraisal of the studies included in the Sponsor submission

The sponsor submission assessed the quality of the included studies based on principles of the Centre for Reviews and Dissemination (CRD), University of York. Different checklists were used to assess RCTs and observational studies, which, in general, seem appropriate.

The randomisation was generally carried out appropriately and the baseline comparability was acceptable in the included RCTs. In the three patient-based RCTs the allocation concealment was unclear (or inadequate), as was the blinding of outcome assessors However, while the blinding of care providers was also unclear, this is something that may not have been possible in the study. In addition imbalances in drop-outs were not reported. [redacted] in the Kristensen study (2011) (full unpublished report available), but was unclear in the Lenhardt et al. (2011) and Schoettker et al. (2012) studies (only abstracts available). Furthermore, [redacted] was conducted in the Kristensen (2011) study, but this was unclear in the studies by Lenhardt et al. (2011) and Schoettker et al. (2012). The EAC team has invited the sponsor to provide the full report for Lenhardt et al. (2011) that had been completed several months ago, however, no further data on this study can be disclosed at this time (see Appendix 3).

In the included case series reports, the sponsor submission considered that patient recruitment was acceptable, and the outcomes were measured accurately, except for Piepho et al. (2010) where they were unclear. For the other relevant quality questions (including identification of confounding factors, completeness of follow-up, and result precision), the answers were always unclear or 'N/A'. Statistical tests were not conducted in the included reports of case series.

3.6 Results

Details on results of each of the included studies were provided in individual tables in the sponsor submission. We present the main results of the included studies in summary tables according to type of studies (manikin-based studies, patient-based controlled studies, and case series reports) (Tables 3.5, 3.6 and 3.7).

3.6.1 Results of manikin-based RCTs

Time to intubation was measured in the three manikin-based RCTs. In the Piepho et al. (2010) study, the time to intubation was slightly longer when using the Ambu aScope compared with the control fibrescope, for both normal and difficult airway scenarios. The mean difference in time to intubation for difficult airway was seven seconds (95% Confidence Interval: -11.66 to 25.66), which was statistically non-significant. Scutt et al. also found that time to intubation was similar between the use of Ambu aScope and the control fibrescope (P=0.18), although the manikins used were not explicitly revised to simulate difficult airways.[10] In the Vijayakumar et al. (2011) study, a difference of 30 seconds in time to intubation between Ambu aScope and fibrescope was considered as a clinically important minimal difference. The

mean difference in time to intubation was ten seconds, and the estimated 95% CI (1.26 to 18.74) did not overlap with the hypothesized difference of >30 seconds.

Piepho et al. (2010) found that intubation success rate was lower when using Ambu aScope compared with using control fibrescope (67% vs. 81%, P=0.02), which was mainly due to the low image quality. Scutt et al. (2010) found that the use of Ambu aScope was associated with more reported problems than control fibrescope (32% vs. 17%, P=0.04), including manipulation, railroading tubes and picture quality. Further, the Ambu aScope was consistently associated with a lower rating score in terms of ease of use and image quality (Table 3.5).

It should be noted that anaesthetists included in the manikin-based studies had previous experience of using standard fibrescope, but lacked experience in using Ambu aScope. Therefore, the differences between Ambu aScope and conventional fibrescope may have been over-estimated in these studies.

Table 3.5. Main results of manikin-based RCTs

Study	Outcomes	Results: Ambu aScope vs. Control	Notes
Piepho et al. 2010. No. of anaesthetists: N=21	Time to intubation (seconds)	Mean (SD): 63 (36.1) vs. 56 (24.5) (P=0.59)	Authors commented that the low image quality may have contributed to the higher failure rate of the Ambu aScope. * P<0.01
	Intubation success	14/21 (67%) vs. 17/21 (81%) (P=0.02)	
	Rating of devices: 1-excellent, 2-good, 3-satisfactory, 4-sufficient, 5-inadequate, 6-fail	Overall (range): 3 (1-5) vs. 2 (1-2.5)* Rigidity: 3 (2-5) vs. 2 (1-3)* Tip articulation: 3 (1-5) vs. 2 (1-3)* Picture quality: 3 (1-5) vs. 2(1-3)*	
Scutt et al. 2011. No. of anaesthetists: N=22	Time to intubation (seconds) – 3 different manikins or 3 different SADs	Mean (SD) Oral without SAD AT: 40 (26) vs. 42 (32) Bill1: 97.1 (80) vs. 78.1 (80) Airsim: 61.9 (45) vs. 45.9 (27) Nasal without SAD AT: 32.2 (15) vs. 24.4 (8) Bill1: 40.5 (27) vs. 60.4 (75) Airsim: 88.2 (92) vs. 59 (32) Intubation via a conduct (SAD) Via cLMA: 38 (45) vs. 24.9 (9) Via i-gel: 18 (5) vs 19.1 (8) Via lLMA: 23.8 (15) vs. 24.4 (7)	Reported problems included manipulation, railroading tubes and picture quality Difference in time to intubation between devices: P=0.18.
	Frequency of reported problems (without SAD)	32% vs. 17% (P=0.04)	
	Rating of usefulness: 0-impossible, to 10-extremely useful (without SAD)	Mean (SD) Overall: 7.7 (2.1) vs. 8.5 (1.5) Ease of use: 7.2 (2) vs. 8.1 (1.6)	
Vijayakumar et al. 2011. No. of anaesthetists: N=75	Time to task completion (seconds)	Mean (SD) 1st attempt: 63 (31) vs. 53 (23) (P=0.008) 2nd attempt: 48 (23) vs. 41 (19) (P=0.01)	For time to task completion, authors rejected the hypothesis of a difference of >30 seconds and accepted the alternative hypothesis that the difference was <30 seconds.
	Number of tip surface collisions	1st attempt: 2.7 (1.9) vs. 2.5 (1.8) 2nd attempt: 2.6 (2) vs. 2.6 (1.8)	
	Ease of use impression rating (0-extremely difficult, to 100-extremely easy)	Mean (SD) 65 (18) vs. 77 (14) (P<0.001)	

SAD: Supraglottic Airway Device

3.6.2 Results of patient-based RCTs

Patient-based RCTs provide the most relevant and valid clinical evidence on the performance of Ambu aScope in difficult airway management. The main results of relevant patient-based RCTs are shown in Table 3.6, to which we also added a new relevant RCT identified by the EAC team (Schoettker et al. 2012).

In the unpublished Kristensen (2011) trial, the difference in total intubation time between Ambu aScope and the control fibrescope was [redacted] (Note: 95% CIs have been estimated by the EAC team).). Although the difference in time to intubation was statistically significant in favour of the control scope (P<0.05), the investigators concluded that it was not clinically important because the difference was likely to be less than the hypothesized non-inferiority margin (120 seconds) (Kristensen 2011). In the newly identified Schoettker et al. (2012) study, the use of Ambu aScope2 was associated with a longer time to intubation compared to control fibrescope (mean difference of 20 seconds, P<0.05). The time to intubation was similar between the use of Ambu aScope and a pre-formed rigid stylet (-9.0 seconds, [redacted]) in the trial by Lenhardt et al. (2011).

As in the manikin-based studies, [redacted] with the use of Ambu aScope was the main problem reported in the patient-based trials. Compared with the control fibrescope in the unpublished Kristensen (2011) study, [redacted]. Similarly, Schoettker et al. (2012) reported that the image quality by Ambu aScope2 was also lower than the control fibrescope. However, the extent to which the intubation procedure itself is affected by the poor image quality of Ambu aScope does not seem great, with [redacted] of cases in the Kristensen (2011) study being unaffected; and 92% in the Schoettker et al. (2012) study being of at least acceptable quality.

Table 3.6. Main results of patient-based RCTs

Study	Outcomes	Results: Ambu aScope vs. Control	Notes
Kristensen. 2011. Sleeping patients with normal airways	Total intubation time (seconds)	[redacted]	[redacted]

N=20 – all Ambu aScope Awake patients with anticipated difficult airways N=40: Ambu aScope N=20 Olympus N=20	[redacted]	[redacted]	[redacted]
Lenhardt et al. 2011. Patients with anticipated difficult airways (ASA=1-3): Ambu aScope N=70 Preformed stylet N=70	Time to intubation (seconds)	95 (63) vs. 104 (100) (P=0.6)	No serious complications encountered Number of patients in each arm is estimated according to the total sample size (N=140)
	No. of intubation attempts	1.1 (0.4) vs. 1.2 (0.6) (P=0.4)	
	Time interval:visualisation to intubation (seconds)	61 (37) vs. 69 (74) (P=0.1)	
	Intubation success	70/70 vs. 66/70	
	Rating: ease of use	Similar	
Schoettker et al. 2012. Patients with difficult airway (simulated by semi-rigid cervical collar) Ambu aScope2 N=50 Fibrescope N=50	Time to intubation	69.5 vs. 49.5 (P<0.05)	EAC team identified; not included in the sponsor's initial submission of evidence, but subsequently provided, as the presentation was made after the submission.
	Ease of intubation	Easy: 30/50 vs. 38/50 Intermediate: 12/50 vs. 7/50 Difficult: 8/50 vs. 5/50	
	Quality of vision	Excellent: 24/50 vs. 49/50 Acceptable: 22/50 vs. 1/50 Unacceptable: 4/50 vs. 0/50	
	Intubation success (in 4 min)	100% vs. 100%	
	No. of jaw-thrust maneuver	16/50 vs. 5/50 (P=0.01)	

	Two attempts required	4/50 vs. 8/50 (P=0.22)	

ASA: American Society of Anesthesiologists physical status

3.6.3 Results of case series

Results of the five case series reported are summarised in Table 3.7. In total the five case series reports included 20 patients requiring PDT in ICUs, (Jamadarkhana et al. 2011; Perbet et al. 2011), 21 patients with anticipated difficult airways (Piepho et al. 2010; Pujol et al. 2010; Vincent et al. 2011), and only two patients with unanticipated difficult airways (Piepho et al. 2010). The new product *Ambu aScope2* was used in two case series studies (Jamadarkhana et al. 2011; Vincent et al. 2011).

Findings from the case series studies indicate that Ambu aScope is generally acceptable in practice. However, poor image quality and the need for lens cleaning were reported. In the study by Vincent et al., the view of anatomical landmarks was poor in two of the eight cases with difficult airways, and the scope could not be removed from the endotracheal tube (ETT) in one case (Vincent et al. 2011).

Table 3.7. Main results of reports of case series

Study (Patient No.)	Results
Jamadarkhana et al. 2011. Ambu aScope2 Patients requiring PDT in ICU N=10	- The average time to set up the scope and monitor was <5 minutes. - The procedure time from needle puncture of the trachea to tracheostomy tube placement ranged from 5 to 10 minutes. - In one patient, the procedure time was 45 minutes due to a tracheal ring fracture and cuff damage of the tracheostomy tube. - All the anaesthesiologists managing the airway reported easy handling and manoeuvrability because of the light-weight design of Ambu aScope. - The operators performing the procedure scored the clarity and quality of endoscopic view (of needle, guidewire, stomal dilatation and tracheostomy tube placement) to be between 8 and 10. - Cardiovascular and ventilatory parameters were not significantly changed during the procedure in any patient. - No complications were reported during use of Ambu aScope.
Perbet et al. 2011. Ambu aScope Patients requiring PDT in ICU N=10	- Seven of ten participants rated the Ambu aScope 'very satisfactory', and three rated it as 'satisfactory'. - The majority of participants rated Ambu aScope 'very satisfactory' or 'satisfactory' across all of the parameters investigated, including guidewire entry into the trachea and endotracheal placement of the tracheostomy tube (see above). - The presence of the screen was deemed useful in all of the cases. - The absence of aspiration was missed in four cases. - In one case, the endoscope was turned off before the end of the procedure and the control of the cannula placement in the trachea

	had to be done with a standard endoscope.
Piepho et al. 2010. Ambu aScope Patients with predicted difficult airways N=3 Patients with unanticipated difficult airway N=2	- Tracheal intubation was possible in all five patients. - Awake fibreoptic intubations, via a nasal route, were performed in three adult patients with predicted difficult airway who required general anaesthesia. Typical landmarks such as the uvula, tongue, epiglottis and larynx were adequately identified. In two cases the videoscope had to be removed during the procedure to allow the lens to be cleaned with a sterile swab. Application of 4ml lidocaine onto the glottis via the built-in channel of Ambu aScope was fast and controlled under direct vision. Advancing the tracheal tube was smooth and easy in all three cases. - Ambu aScope was also used in the management of two patients, via an oral route, with unanticipated difficult airways for whom fibre-optic intubation was indicated. In one case, airway secretions obstructed vision via the LCD screen. This was resolved following suctioning and cleaning of the Ambu aScope lens using a sterile swab. All anatomical landmarks were identified and the videoscope was advanced smoothly through the glottis following which the tube was advanced into the trachea.
Pujol et al. 2010. Ambu aScope Patients with predicted difficult airways N=10	- Nine of ten intubations with Ambu aScope were performed and completed without incident. Intubation could not be accomplished in one patient within the 30 minutes permitted. Although an adequate view of the glottis was obtained with the Ambu aScope and the carina was reached, a 7.5mm tracheal tube could not be advanced through the vocal cords. - The device was easy to insert in nine of ten patients and difficult to advance due to resistance in one patient (the same patient in whom difficulty in passing the tracheal tube into the trachea was experienced). In all ten patients, a complete view of the glottis was obtained. The image quality was considered adequate in five patients and poor in five. Fogging of the lens occurred in six patients and was cleared easily by gently touching the airway mucosa in four and by removing the scope and cleaning the tip in two. In two cases there were secretions that could not be suctioned but they did not result in difficult tube insertion. Optimal distribution of local anaesthetic over the glottis was achieved in all patients. Tube insertion was easy in eight patients and easy but with some manoeuvres needed in one patient and impossible in one patient.
Vincent et al. 2011. Ambu aScope2 Patients with anticipated difficult airways N=8	- Primary outcome; intubation success: All eight patients were intubated awake successfully using Ambu aScope2; six of eight patients were intubated at the first attempt and the other two patients at the second attempt; seven of eight patients were intubated by the nasal route and one patient orally. - Primary outcome; time for scope position: Mean (range) time to visualize the carina (Tp) was 254.5 seconds (62-540 seconds); mean (range) time for confirming position of the tube in the trachea after visualizing carina (Ti) was 51.5 seconds (44–60 seconds). - Secondary outcome; performance: In six of the eight uses, an excellent view of anatomical land marks was reported, and in two the view was reported as poor, but sufficient for intubating the trachea. Mean score for manoeuvrability was 6.8 (range 3–9). During one use the scope could not be removed from the ETT, but could be removed very easily after the other seven uses. Mean score for usefulness of the scope was 7.4 (3-10)

3.6.4 Results of supplementary studies

In addition to the six excluded studies, four abstracts (Austin et al. 2011; Gernoth & Genzwuerke 2010; Kristensen et al. 2010; and Saumande et al, 2010) were not included in the submission. Reasons for not including the four supplementary studies were not explicitly described in the sponsor's submission. However, the sponsor considered that these four studies provided some supplementary information and presented them in the appendices to the sponsor's submission.

Of the four supplementary studies, three were small-scale case studies and one was a manikin-based study (Table 3.2). Two of the four supplementary studies aimed to use Ambu aScope for endoscopic monitoring during PDT in ICU (Austin et al. 2011, Gernoth & Genzwuerke 2010). Kristensen et al. (2010) used Ambu aScope for endoscopic intubation in five patients with difficult airways. The manikin-based study (Saumande et al. 2010) compared Ambu aScope alone and Ambu aScope in combination with Airwayscope (Table 3.2). Results of these supplementary studies are summarised in Table 3.8 below. Findings from the four supplementary studies were generally similar to that from the included RCTs and case series studies.

Table 3.8 Main results of supplementary studies

Study	Design / Objectives	Results
Austin et al. 2011. Abstract	- Design unclear (n=5). - ICU: using Ambu aScope for endoscopic monitoring during PDT.	- Mean duration of use was 21 minutes. - No complications directly attributed to Ambu aScope. - Compared with conventional fibreoptic scopes, Ambu aScope was rated higher for time to, and ease of, set-up, and grip/ease of use; but lower for the ability to manipulate the tip, a tendency for picture fog and blur, and lack of section.
Gernoth & Genzwuerke 2010. Abstract	- Case study (n=4) - ICU: using Ambu aScope for monitoring PDT	- Handling and positioning of Ambu aScope through the orally placed tubes (ID 7-8mm) was easy and provided a good view – identification of relevant structures could be obtained in all patients within 30 seconds. - In all cases, PDT could be accomplished smoothly with good endoscopic view on monitoring. - Total mean endoscopy time was 18 minutes.
Kristensen et al. 2010. Abstract	- Case study (n=5) - ET intubation: patients with difficult airways.	- All five patients were intubated successfully with Ambu aScope while awake.
Saumande et	- Manikin-based (simulated difficult	- First attempt successful: Ambu aScope + AWS 10/10

al. 2010. Abstract	airway). - Ambu aScope vs. Ambu aScope + AWS (Pentax Airwayscope) - Ten anaesthetists performed 20 endoscopic intubation (EI) procedures	vs. Ambu aScope 5/10. - Mouth-glottis time (seconds): Ambu aScope + AWS 6 (1-13) vs. Ambu aScope 37 (5-89). - Mouth-carina time (seconds): Ambu aScope + AWS 15 (10-30) vs. Ambu aScope 110 (43-214). - Total time of EI (seconds): Ambu aScope + AWS 69 (48-81) vs. Ambu aScope 140 (70-265). - Checklist score: Ambu aScope + AWS 3.3 vs. Ambu aScope 1.9 - Global rating scale: Ambu aScope + AWS 4.5 vs. Ambu aScope 3

3.7 Does each relevant study include the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope?

3.7.1 Patient population included

Relevance of manikin-based studies to real patients with difficult airways is contested. The most relevant and valid evidence was from three patient-based randomized controlled trials. However, of the three RCTs, two included patients with anticipated difficult airways (Kristensen 2011; Lenhardt et al. 2011), and one included patients with simulated difficult airways (immobilised neck with semi-rigid cervical collar) (Schoettker et al. 2012). Two case series included patients who required PDT in ICUs (total N=20) (Jamadarkhana et al. 2011; Perbet et al. 2011). None of the available trials included patients with unanticipated difficult airways, and no studies were explicitly conducted in A&E departments. Therefore, it is uncertain whether the results of the included studies could be applied to “patients with unexpected difficult airways requiring emergency intubation including awake or anaesthetized patients with displaced tracheostomies”, as specified in the final scope. One of the studies did not use the counterfactual identified in the scope (Lenhardt et al. 2011).

3.7.2 Interventions investigated

The previous version of the product, Ambu aScope, was evaluated in three manikin-based studies, two of the three RCTs (total N=90), and in three of the five case series studies (total N=25) (Table 3.1). The revised version, Ambu aScope2, was evaluated in only one controlled trial (total N=50), and in two case series (total N=18). According to the sponsor submission, “Ambu aScope2 is the same product with a

number of enhancements that include an easy clearing membrane, flow connector and the removal of time-out features on the single-use scope", so evidence from studies of Ambu aScope should be relevant to the assessment of Ambu aScope2. A product validation memorandum (Appendix 10) indicated that the new lens performed similarly in animal testing compared to a competitor lens. Animal testing also suggested the flow connector added to the Ambu aScope performed without problems enabling the supply of oxygen or air through the working channel.

3.7.3 Comparators used

The specified relevant comparators are reusable flexible endoscope (fibrescopes using fibre-optic technology or video scopes using video technology). The comparators used in the controlled trials appropriately included reusable fibrescopes manufactured by Storz, Pentax, or Olympus. However, in the study by Lendhart et al. (2011), Ambu aScope was combined with GVL, and the comparator was a combination of GVL and a preformed rigid stylet, which limited the relevance of its results.

3.7.4 Outcomes measured

The outcomes measured in the included studies included intubation success rate, time to intubation, ease of use, and image quality. These outcomes are relevant to the outcomes specified in the final scope. However, there is no direct evidence on clinical consequences associated with the use of Ambu aScope. None of the included studies were primarily designed to evaluate the safety and adverse events, nor was this a realistic prospect from a statistical perspective.

3.8 Description of the adverse events reported by the sponsor

In the sponsor submission, detailed search strategy for adverse events was reported on Section 10.2 Appendix 2.

The adverse event searches were conducted on the same resources as the clinical evidence searches, using the same date limit (1992-2012) and the same search strategy as discussed in appendix 1 (10.1). Similarly the additional searches of ASA, ESICM, ESA and STA to identify abstracts were considered suitable to locate information relating to adverse events.

The FDA's MAUDE database was searched for any adverse event reports relating to the Ambu aScope. In Section 7.7.3 the sponsor reports that no such reports were located when the database was searched on 15th May 2012. However, the sponsor submission did not mention the search of the MHRA.

The EAC would consider the search, combined with screening of references located by the clinical evidence searches, an adequate strategy to locate adverse events information, provided the MHRA website has been searched. The sponsor has confirmed this was done.

In the sponsor submission, the sponsor stated that they did not identify any studies that were primarily designed to assess safety and adverse outcomes. The sponsor claimed that they are not aware of any adverse events caused by the use of Ambu aScope. The studies included in their report did not note any serious adverse events specifically associated with the use of Ambu aScope, other than the reported lower rating of ease of use and lower image quality than standard reusable fibrescopes.

The most important adverse events are clinical consequences associated with delayed or failed intubation. It is crucial to interpret the longer time to intubation with the use of Ambu aScope, compared to the standard reusable fibrescope. For example, the difference in total intubation time was 55 seconds (95% CI 5.8 to 104.4) in the unpublished patient-based trial by Kristensen (2011). Although the investigators of the trial stated that such a difference was not clinically important, other expert advisers may have different opinions. It is plausible to argue that this longer time, even if not *of itself* important, is nevertheless a surrogate for greater difficulty and hence potential complications.

According to findings from the included studies, the success rate of intubation assisted by the use of Ambu aScope was satisfactorily high (nearly 100% in patient-based studies). However, the evidence available was mainly from studies of patients with anticipated difficult airways. It is unclear whether the intubation success rate would remain high in patients with unanticipated difficult airways requiring emergency intubation. If not, failed intubation could result in serious clinical consequences, including death and hypoxic brain injury.

3.9 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

In the sponsor submission, a quantitative meta-analysis was not conducted. This is appropriate and justifiable because of the large heterogeneity across studies in terms of study participants, clinical setting, comparators used, and outcomes measured.

Results of relevant studies were descriptively summarised in the sponsor submission. The overview of the clinical evidence in the sponsor submission was clear and generally appropriate.

In the sponsor submission the sponsor summarised the clinical evidence and concluded:

- "Similarly high rates of intubation success and times to intubation were observed between Ambu aScope and conventional reusable scopes." (*EAC commentary: depending on what should be the minimal clinically important difference, since the point estimates favoured reusable scopes.*)
- "In addition to providing acceptable visualization of anatomical structures, aScope was considered easy to use and manoeuvre, as well as being useful." (*EAC commentary: ease of use and picture quality were rated to be lower, but possibly still acceptable for Ambu aScope*).
- "aScope is, therefore, a suitable alternative to reusable scopes for facilitating tracheal intubation in patients with difficult airway and for those requiring PDT."
  (*EAC commentary, Ambu aScope 2 is likely to be a suitable alternative to reusable scopes for anticipated difficult airway management. There are no clinical evdiecne on the use of Ambu aScope2 in patients with unanticipated difficult airways.*)
- "This ready-to-use, single-use device negates the issue of availability, minimizes the risk of infection and cross-contamination, and eliminates the delays and possible damage associated with reprocessing of reusable scopes."
  (*EAC commentary: there is no direct clinical evidence to support this statement, but such evidence would be very hard to acquire.*)

3.10 Additional work carried out by the External Assessment Centre in relation to clinical evidence

EAC reviewed sponsor search strategies and attempted to re-run them but found it impossible to do so precisely due to lack of necessary information for all of the databases.

The EAC expanded the searches for unpublished literature used by the sponsor and identified a new ongoing study and a new conference abstract that presented results of a patient-based RCT (the abstract was subsequently provided by the sponsor, as the presentation had been made after the initial submission of evidence). In addition, we identified duplicates of the same study which were not included in the sponsor submission. Because of this additional work, the clinical evidence base is now more

complete and less contaminated. However, the direction of conclusions has not been affected.

The EAC also conducted a brief search on delayed or failed intubation of scope and identified 258 references (MEDLINE only) (see Appendix1).

Results of non-inferiority trials were re-analysed to estimate 95% confidence intervals for differences in time to intubation between Ambu aScope and fibrescope. The 95% confidence intervals are important for interpreting results of non-inferiority studies, which were not provided in the sponsor submission.

3.11 Conclusions on the clinical evidence

The available clinical evidence is rather limited in terms of patients included, interventions evaluated, and outcomes measured. The number of patients included in the relevant studies was very small. There is a lack of details on design and results because most of the relevant studies are unpublished or available only as meeting abstracts. Non-inferiority margins were defined very differently in the included studies without any justification.

According to the available clinical evidence, Ambu aScope has relatively low image quality and is associated with relatively longer time to task completion than reusable flexible endoscopes. Nevertheless, it can be concluded that Ambu aScope is possibly an ***acceptable*** alternative to reusable endoscopes for facilitating tracheal intubation in patients with difficult airway and for those requiring PDT. The main clinical evidence is further clarified below:

- Time to intubation: Time to intubation was slightly longer when using Ambu aScope compared with conventional reusable fibrescope, although the difference may not be clinically important.
- Image quality: Low image quality with the use of Ambu aScope was the main problem reported in both patient-based and manikin-based studies, compared with reusable endoscopes. However, the poorer image quality with the use of Ambu aScope has little impact on the intubation procedure itself.

The available evidence indicated that Ambu aScope is a clinically acceptable alternative to reusable endoscopes for facilitating tracheal intubation in patients with difficult airway and for those requiring PDT.

Before coming to a definitive conclusion on the acceptability of the single-use scope, some remaining uncertainties about the reliability and generalisability of the clinical evidence needs to be resolved.

It is still unclear about what the minimal clinically important difference in the time to intubation between Ambu aScope and reusable fibrescope should be. Clinical experts pointed out that maintenance of oxygenation is the primary aim and small differences in intubation time would not be clinically important. Other factors that could be important are operator's experience and the learning curve associated with use of the Ambu aScope, and the inability to use an Aintree catheter, thus precluding a technique in which all anaesthetists should be competent. Delayed access to a reusable scope, however, must be set against this. Larger patient series are required to answer these questions.

The available evidence was mainly from studies of patients with anticipated difficult airways. It is unclear whether the intubation success rate would remain high in patients with unanticipated difficult airways requiring emergency intubation. It is this latter group that are most relevant to question 2.

Please note the following crucial point before turning to the economic evidence. The effectiveness described above relates to a comparison between two device types assuming that both are available – i.e. question 1. In turning to the next section we deal with question 2, which considers the differences in outcome contingent upon differential *availability* by type of device – the authors compare the costs of both devices and compare effectiveness, So effectiveness in question 2 relates to differences in outcomes contingent on different levels of availability if money is spent procuring one type of device instead of the other. All the considerable evidence above does nothing to tell us what different procurement policies yield in terms of relative availability, never mind clinical effects contingent on availability differences.

4. Economic evidence

4.1 Critique of the sponsor's search strategy

The search methods for existing economic evidence are detailed in Section 8.1 of the sponsor submission and the detailed strategies listed in Section 10.2 of Appendix 3.

The sponsor searched appropriate databases (MEDLINE, MEDLINE In Process, EMBASE and NHS EED) for economic evaluations and the date ranges and platforms used in the search are documented. Keywords (free text?) were used to search on title and abstract. Given the stated aim of maximising the sensitivity of the search, restriction by publication type was not used. However, searches for existing economic evaluations were restricted to English language only. It was not made clear why language restrictions were placed on the search for economic evidence while there were no such restrictions on the searches for clinical evidence, though the limiting factor lies in the scanty nature of the clinical evidence.

As with the clinical searches, reference lists of all relevant studies were searched to identify additional references.

Figure 4 in the sponsor submission provides a flow chart for economic studies – 465 studies in total were located via databases, plus one via other sources. Of the 466 records, 343 were left after removal of duplicates, but only three of these remained after screening for inclusion in the qualitative synthesis.

In addition to MEDLINE, EMBASE and MEDLINE In Process, the sponsor also searched NHS EED. The search platform is listed as Ovid for all databases, although the EAC assumes NHS EED was searched either via Cochrane (Wiley) or CRD (Centre for Reviews and Dissemination). The searches were conducted on 1st June 2012 and the dates covered were 2002-2012. The difference between dates that they searched for clinical evidence and economic evidence is not explained, but may relate to dates the technology became available.

The search strategy is reproducible and essentially combines the terms used to describe the procedure and the technology in the clinical evidence searches. The device names ("Ambu" or "ambuscope" or "aScope") are omitted from the strategy, such that some relevant references may have been missed if the broader technology terms failed to locate them. As with the clinical evidence searches, the term "fibre*" is used where "fiber*" would also be needed to pick up references to "fiberscope" or "fiberoptical tracheal intubation" for example.

The strategy would have been improved by broadening the terms designed to pick up economic evaluations – only the term "cost*" is used here, which ought to have been supplemented by other appropriate terms (e.g. "econom*", "budget*", "price*", "expenditure"), or an appropriate search filter. Again, however not too much should be made of the impact on sensitivity.

In the sponsor submission, the searches were limited to the last ten years (2002 onwards) and were restricted to English language. No explanation has been given on the decision to limit to English language only while the clinical evidence searches had no language limits.

All these factors may have reduced the sensitivity of the strategy to retrieve economic evidence in the sponsor submission; although given the relative novelty of the technology the number of such studies is likely to be small.

The EAC conducted a trial search to test whether broadening the strategy might locate additional relevant references. An extra 30 references were thus identified (see Appendix 2). We read the abstracts of these, but did not find any additional papers that were relevant.

4.2 Critique of the sponsors study selection

The sponsor selected health economic studies using specified inclusion and exclusion criteria based on the decision problems specified in the final assessment scope. The inclusion and exclusion criteria were appropriate and consistent with those used to select clinical evidence.

4.3 Included and excluded studies

The three economic studies were included in the sponsor submission (Table 33). However, EAC identified one additional study conducted by Norris et al. (2010) that was presented (poster format) at the DAS conference, 2010. It was listed on the sponsor website, and also mentioned in Section 9.3.4 (page 144) of the sponsor submission, but was not included in their review. This is an ongoing study and was excluded from the sponsor's review as it was a simple, preliminary cost analysis. We included this study and summarised all four studies in Table 4.1 below.

Table 4.1. Included economic studies

Study	Country	Design	Population	Intervention(s)
Gupta et al. 2011.	USA	Cost study	N/A	Reusable scope
Tvede et al. 2012.	Denmark	Cost study	N/A	Single-use vs. Reusable scope
Liu et al. (2012).	USA	Cost study	N/A	Reusable scope
Norris et al. 2010.	UK	Cost study	N/A	Reusable scope

4.4 Overview of methodologies of all included economic studies

All studies focused on estimating cost of the Ambu aScope and/or reusable flexible scope. No study considered economic effects of any changes in patient outcome.

One study compared Ambu aScope with reusable flexible scope (Tvede et al. 2012). They estimated direct costs associated with both scopes in terms of equipment, maintenance, repair and staffing.

The other three studies (Gupta & Wang 2011; Liu et al. (2012); Norris et al. 2010) were strictly non-comparative. The study by Norris et al. (2010) investigated the cost of fibre-optic intubation and its associated costs from maintenance, repair and replacements. They concluded that the cost of fibre-optic intubation was £32,000 with 141 procedures performed in 2008 to 2009. This led to an average of £227 per intubation using fibre-optic scope. Norris et al. (2010) stated that the price of a disposable, single-use scope during the study period had an initial price of £200 to £300. The EAC drew the conclusion that the reusable scope would be no more expensive than single-use ones.

The sponsor did not derive any conclusions from these studies.

4.5 Overview and critique of the sponsor's critical appraisal for each study

The economic studies were reviewed using the quality assessment checklist conducted by Drummond and Jefferson (1996) for economic evaluation studies.

4.6 Does the sponsor's review of economic evidence draw conclusions from the data available?

The submission included a summary of the findings of the three studies in Table 33 of the sponsor submission. We added the study identified by EAC, which was the only study to compare the costs of Ambu aScope with an alternative in the UK setting.

Tvede et al. (2012) estimated the total cost of an intubation using either Ambu aScope or reusable scope over a one year period. The costs associated with each of the scopes consisted of device acquisition and staffing. In addition, they investigated the additional costs for reusable scopes, including repair and maintenance. They estimated the cost of an intubation for using Ambu aScope at €204 (~$266, ~£170) and for reusable scope at €178 (~$232, ~£148).

The two studies conducted by Gupta and Wang (2011) and Norris et al. (2010) were based on the estimations of cost of an intubation using a reusable scope in current practice to attempt to justify the price of Ambu aScope. The average costs of a reusable scope were $120 (~€95, ~£78) in the study by Gupta & Wang (2011) and £227 (~€276, ~$340) in the study by Norris et al. (2010).

The study conducted by Liu et al. (2012) identified costs associated with the use of a reusable scope for tracheal intubation in an academic anaesthesia department, including acquisition, repair, cleaning, and staffing. The average cost for use of a reusable scope was calculated as $95 (~€75, ~£61) per intubation.

The estimated costs of a reusable scope for an intubation were very different (~£148, ~£61, ~£78 and £227). This might be explained by the differences in the methods used for collection of cost data (such as acquisition costs), the number of procedures used per scope, the maintenance and repair costs, and the lifetime of a reusable scope.

The comparison study (Tvede et al. 2012) suggests that the net costs per patient intubation are similar in reusable and reusable devices, though marginally favouring reusable devices. However, the other studies show that cost estimations are unstable, varying widely from study to study.

4.7 De novo cost analysis

The *de novo* cost analysis submitted by the sponsor aimed to estimate the costs and consequences associated with the use of Ambu aScope2 and with reusable, flexible endoscopes. It was supported by a Microsoft Excel spreadsheet model.

4.7.1 Patients

The cost analysis was conducted in relation to patients with unexpected difficult airways requiring emergency intubation including awake or anaesthetised patients with displaced tracheostomies, including adults or children who have been clinically evaluated for endotracheal tubes size 6 or above.

4.7.2 Technology

The technology in question is Ambu aScope2, a hand held single-use flexible intubation videoscope for visual guidance during intubations.

4.7.3 Comparator(s)

The selected comparator was reusable endoscopes. The sponsor rightly highlighted that this includes both fibrescopes and videoscopes, encompassing a range of technologies and costs. The technology used is likely to vary with the nature of "difficult airways" and the context and setting.

In the sponsor's current cost model, the sponsor considered the comparison of Ambu aScope2 and reusable scopes in the scenario of unexpected airway problems. They estimated the difference in costs comparing Ambu aScope with reusable scopes in the situation where airway problems required emergency intubation guided by fibrescope.

The NICE scope committee concluded that a relevant model of care might include the complementary use of reusable scopes and the Ambu aScope in different clinical scenarios (page 7 of the NICE Scope). The sponsor's current model did not compare the alternative in which Ambu aScope 2 could be used in a complementary role with reusable scopes.

4.7.4 Model structure

Two simple models were developed in the sponsor economic submission to estimate the costs and consequences associated with the use of Ambu aScope2 compared with reusable flexible endoscopes in unexpected difficult airway requiring emergency intubation and dislodged tracheostomy respectively.

The model structures are clearly presented in two schematic diagrams supplemented by a Microsoft Excel spreadsheet (figures 5 and 6 in the sponsor's submission). The models are decision analytic models with very simple structures. They clearly represent what the model was designed for, and are consistent with the text in the report. The EAC reproduced the model structures as shown in Figures 4.1 and 4.2.

The clinical pathways for both Ambu aScope2 and reusable scopes shared the same structure but differed by the rates of delay/failure intubation and risk of brain injury or death (see assumptions in next section).

Figure 4.1. Model of unexpected difficult airway-requiring intubation.

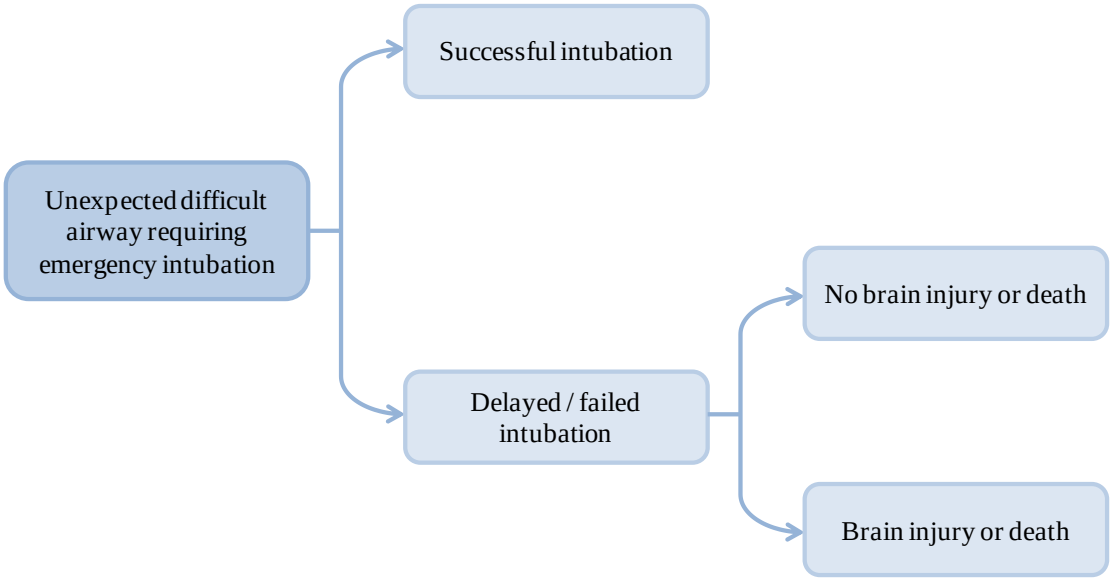
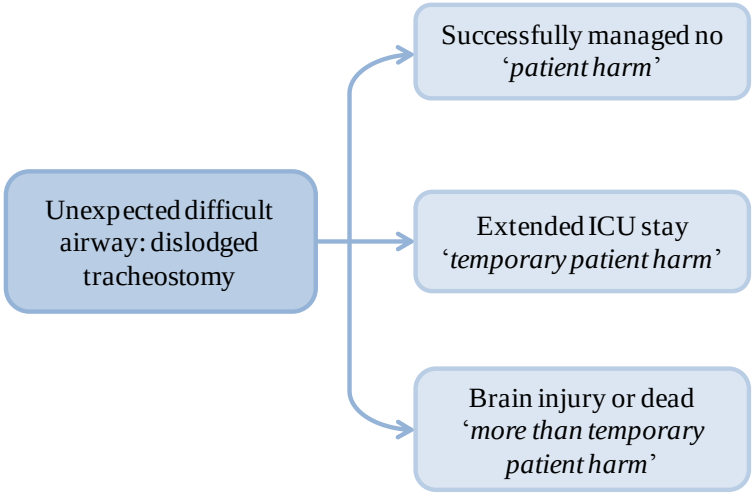


Figure 4.2. Model of unexpected difficult airway – dislodged tracheostomy



The model deals with a scenario where urgent intubation or re-siting of a tracheostomy tube is required. It is based on a strong assumption that was not justified in the previous section of the submission – namely that a policy of using single-use devices will reduce the chance that the necessary scope will not be available in one of the above urgent scenarios. Since there is no evidence for this,

nor any compelling argument about why it might be so, the entire model is built on insecure foundations.

In both cases it is properly assumed that the delay or non-availability of a reusable scope will have adverse effects on clinical outcomes. However, it is assumed that single-use scopes will be available and thus the adverse effects of delay will be reduced as compared to a policy of procuring reuseable devices. However, after dealing in huge detail with the direct comparisons of the device types, no evidence or even considered argument is produced to say that procuring single-use devices in place of reusable devices mitigates the availability problem. In the absence of other evidence, the EAC has approached a number of clinical experts for their advice (see Appendix 3). While the clinical experts differed in the detail of their views of the functionality of Ambu aScope2 when compared with reusable scopes – preferring reusable scopes where available – there was consensus that there might be occasions where delays in accessing reusable scopes was possible and that, in these circumstances, a more immediately available Ambu aScope2 would be preferable. Some arguments were offered to say why a policy of procuring reusable devices (Policy 1 – see Section 1.5) might improve availability. One related to the need to obtain the monitor in the case of reusable devices and the other to non-availability during re-sterilisation. However, stock control is not perfect at hospital or operating theatre/ward level, and so single-use devices equally might not be available after disposal.

The EAC believes that the sponsor's model structure is defective, as it does not clearly address the availability issue, which is crucial to the comparison of reusable and single-use scopes. Instead, the model proceeds on the assumption that a single-use scope (and of course associated monitor) will be available without clinically important delay, but offer no justification for this. The EAC suggest an alternative model structure in Section 4.12 (Figure 4.3), which specifically includes a comparison of single-use and reusable scopes, and a more closely specified pathway.

4.7.5 Clinical parameters and variables

4.7.5.1 Clinical parameters

In the sponsor submission, Section 9.2.1, the sponsor stated that evidence from clinical trials of Ambu aScope has not been used in the cost analysis. However, two clinical outcomes were specifically used in the sponsor models and the costs associated with those clinical parameters were investigated. These were firstly the rates of delayed/failed intubation and the management of dislodged tracheostomy; and secondly the relative risk of such events for Ambu aScope compared with reusable ones, and hence the harm (brain injury / death) caused by it.

For the first parameter in the sponsor submission, the sponsor stated that these rates are difficult to estimate accurately from the literature. While rates of failed intubation were reported in a recent Royal College of Anaesthetists NAP4 (2011) audit report, this was not specific to patients with difficult airways. They relied on older cohort studies for these estimates, dating from 1992 and 1994 respectively (Rocke et al. 1992; Rose & Cohen 1994).

The EAC considered the possibility that these two early studies might no longer represent current clinical status in this area. It is possible that rates have improved with technological change and innovations in practice since then. Experts did not offer a view on this point. The EAC conducted a brief search of MEDLINE (Ovid) 1946 – June week 3 2012 for studies reporting on the topic of delayed or failed intubation. This search located 258 references, and the search strategy is described in Appendix 1. We recommend review of this information, which would be a considerable task and is outside the scope of this report.

For the second key clinical parameter in the sponsor submitted model, the relative risk of Ambu aScope was compared with reusable alternatives. In the sponsor submission, the sponsor properly stated that no evidence was available in relation to the proportion of events that could be avoided with Ambu aScope2 through its more immediate availability. This has been modelled by assuming an exploratory reduction (10% at base case) in the risk of delayed/failed intubation and a similar reduction in the risk of patient harm in the context of dislodged tracheostomy.

The figure of 10% is arbitrary, and there is no direct evidence bearing on the question. It is worth noting that this figure is multiply contingent. Firstly the difficulty has to arise as discussed above. Then there has to be a difference in availability (Policy 1 – see Section 1.5), and then this difference has to be sufficient to cause hypoxic brain damage (Policy 2 – see Section 1.5). The 10% above is the product of

probability 2 and probability 3. Suppose a device is available 90% of the time under Policy 1 (Ambu aScope2) and 70% of the time under Policy 2 (reusable scope). Suppose further that when difficulty is encountered, brain damage results one time in 50. Then the 'effectiveness' of the optional ordering policy (Policy 1) is 0.4% (rather than 10%). Even if damage occurred one time in 20 (which seems very high), then effectiveness would be 1% (an order of magnitude less than suggested by the sponsor).

4.7.6 Resource identification, measurement and valuation

4.7.6.1 Technology and comparators' costs

Resource use associated with the management of difficult airways was described in Section 9.3.3 of the sponsor submission. The sponsor stated that they conducted a systematic review to identify relevant cost study and that there is no cost study in the UK setting. The sponsor therefore conducted a survey in NHS centre to collect the data on devices and associated costs.

The survey collected information relating to the costs of equipment and maintenance. The acquired equipment costs of videoscopes are substantially more expensive than fibrescopes. In the sponsor model the sponsor stated that they were not able to present separate analyses for the two types of technologies, fibrescopes and videoscopes. Average costs of equipment over the survey centres were used in their model. This uncertainty was explored in sensitivity analyses.

Unit costs used in the model included the Ambu aScope, reusable scope, and ICU and hospital length of stay due to failure of intubation or a dislodged tracheostomy.

4.7.6.2 Costs used in submitted models

Cost associated with stay in ICU for failure intubation

- 6.2 days in ICU (HES T884);
- Unit NHS critical care reference cost (2010/2011) of per day in ICU (levels 2-3) – £1321;
- Total cost: **£8190**.

Cost associated with stay in ICU for dislodge tracheostomy

- 15.4 days in ICU (HES T424);
- Unit NHS critical care reference cost (2010/2011) of per day in ICU (levels 2-3) – £1321;
- Total cost: **£20343**.

4.7.6.3 Costing of the technology

The cost of Ambu aScope2 was identified as £179 per single-use scope. Additionally to use the Ambu aScope2 a monitor is also required. Although this has a list price of £799 it is currently supplied free with a “starter pack” and replaced in event of fault or damage.

The EAC believes that reflects current pricing structure. However, it could be envisaged that this would change with market penetration. At present a started pack of five Ambu aScope2 scopes includes a monitor that will be replaced free of charge should it fail. The shelf-life of the scope is three years.

4.7.6.4 Costing of the comparator

The sponsor conducted a survey of NHS centres to obtain costing information on reusable scopes. Costs of reusable scopes included equipment costs, maintenance costs, and costs associated with reprocessing (which might be centre and local, in both cases difficult to obtain) and storing the equipment prior to use.

While a survey would potentially yield useful information, a response was received from only six out of 20 centres and the reported costs varied widely. Only two centres processed scopes locally and repair and maintenance costs were difficult to obtain.

The EAC noticed that no information was provided on the sampling frame or sample selection method, nor on the rationale for a sample size of 20. Only six centres responded on time. The EAC questions the representativeness of the estimated costs based on only six centres. Nevertheless, some real life NHS data were collected to inform the analysis.

Cost estimation presents substantial difficulties. The sponsor supplied detailed survey data from six NHS centres after reading the EAC draft report and at request from NICE. The EAC appreciated the detailed information and efforts that the sponsor had made. Given the limited time to prepare their report and to obtain responses from NHS centres, the EAC is satisfied that these were the best data available for estimating costs of reusable scopes in NHS centres.

However, great uncertainty remains as to the general applicability of the base case cost specified, particularly as costs may also vary according to the lifespan of the scope, the number of scopes held, and the uses to which they are put.

Detailed critique of input values and assumptions of the sponsor’s model are detailed in Table 4.2.

Table 4.2 Critique of model input values and assumptions of sponsor's model

Assumption	Value	Justification	EAC Comments
Number of procedures performed *per annum* with reusable scopes (base case).	150	The number of procedures performed with reusable scopes is a key variable in the cost analysis since it determines the cost per use of a reusable scope. However, this varies widely by NHS institution and setting. A base case was selected to reflect data collected in a survey of NHS centres and this assumption was varied in sensitivity analyses (Data from sponsor).	Acceptable.
Costs of reusable flexible intubation scope (weighted costs including stack systems, cameras, etc).	£12,105	Each NHS centre has a unique set-up in terms of reusable equipment. An NHS survey was used to estimate the average cost per reusable scope, including the acquisition costs for scopes and related equipment, such as stack systems and cameras. This cost is varied in sensitivity analyses (Data from sponsor).	Acceptable. However, great uncertainty is associated with these estimated input values. The costs of equipment for fibrescopes and videoscopes are substantially different and should be estimated separately.
Annual maintenance and repair costs of reusable flexible intubation scope – proportion of equipment acquisition costs.	0.21	Maintenance costs (including any repair costs) were collected using the NHS survey (Data from sponsor). Data on maintenance and repair were very difficult to collect, however, in one centre good information was available. This was used to estimate the proportion of a piece of equipment's acquisition cost that is spent on maintenance and repair on an annual basis (Data from sponsor).	Acceptable.
Number of reusable scopes available.	5	The base case number of scopes reflects the results of a survey in NHS centres and is varied in sensitivity analyses (Data from sponsor).	Acceptable.
Assumed lifetime of reusable scope equipment.	5 years	This reflects the literature (Drummond et al. 2005) and is varied in sensitivity analyses.	Acceptable.
Endoscopic reprocessing costs (per scope reprocessed)	£35	The majority of NHS centres surveyed (n=4/6) used a central reprocessing centre. A standard cost is charged per item reprocessed. In the base case we have used the mid-point of the costs quoted for central reprocessing.	Acceptable.

		Other centres reprocess scopes locally, for example in the department. This has been considered in sensitivity analyses using NHS survey data on the staff and time involved in reprocessing, as well as the costs for equipment (Data from sponsor).	
Rate of delayed/failed intubation in unexpected difficult intubation patients: Operating Theatre setting – reusable scopes.	0.0625	Available trial data suggests that there are no significant differences between scopes in terms of intubation outcomes. However, the available trial data does not correspond to the setting defined in the decision problem, i.e. unexpected difficult airways. Rates of intubation failure in difficult intubation patients were therefore identified in the literature (Rocke et al. 1992) and varied in sensitivity analyses.	A systematic review / comprehensive review should be conducted to inform this input value. The early studies might no longer represent current clinical status in this area. It is possible that rates have improved with technological change and innovations in practice since then. A comprehensive literature review should be conducted to inform choice of the input parameters. The EAC conducted a brief search of MEDLINE (Ovid) 1946 – June week 3 2012 for studies reporting on the topic of delayed or failed intubation (search strategy described in Appendix 1). This search located 258 references.
Rate of delayed/failed intubation in unexpected difficult intubation patients: ICU setting – reusable scopes.	0.166	Estimates for failed intubation in difficult intubation patients on the ICU were not available. The upper estimate of the range for general anaesthesia was used in the base case.(Rose & Cohen 1994)	Same as above.
Rate of brain injury and death in difficult intubation patients where intubation has failed	0.28	No data on outcomes related to delayed/ failed intubation were available from clinical trials for any of the technologies. Data on rates of brain injury and death in the relevant population and settings were taken from the literature and varied in sensitivity analyses (Thomas & McGrath 2009).	Same as above.
ICU length of stay – failed intubation	6.2 days	HES data was investigated to identify relevant patient episodes and associated length of stay estimates. Failed	Acceptable.

		intubation data were reviewed and ICU stays were estimated from available data (Data from sponsor).	
Rate of ICU admission or prolongation of stay – failed intubation	0.75	A published survey (Thomas & McGrath 2009) of patient safety incidents was used to estimate the rate of ICU admission (or patients where ICU stay was prolonged).	Acceptable.
Rate of brain injury or death in patients with dislodged tracheostomy	0.13	A published survey (Thomas & McGrath 2009) of patient safety incidents was used to estimate the rate of brain injury or death.	Acceptable.
Rate of ICU stay or prolongation of stay – dislodged tracheostomy	0.75	The rate of ICU stay with dislodged tracheostomy was based on a recently conducted survey of tracheostomies.(McGrath & Thomas 2010)	Acceptable.
ICU length of stay – dislodged tracheostomy.	15.4 days	HES data was investigated to identify relevant patient episodes and associated length of stay estimates. Revised tracheostomy data were reviewed and ICU stays were estimate from available data (Data from sponsor).	Acceptable.
Assumed reduction in events with Ambu aScope2.	10%	Exploratory assumption, varied in sensitivity analyses.	This is an assumption made for exploratory analysis. We have found no evidence to support this, or to suggest a different value.

HES = Health Episode Statistics; ICU = Intensive Care Unit.

4.7.7 Sensitivity analysis

The submission carried out one-way deterministic sensitivity analysis to explore parameter uncertainty and the effect of those changes on the incremental cost of the Ambu aScope. One-way analyses were conducted by varying the failure rates of intubation, reduced risk rates of failed intubation by Ambu aScope, length of hospitalisation, and the costs associated with reusable scopes including equipment, maintenance, equipment lifetime, and reprocessing.

The value for each parameter in the sensitivity analysis ranged within +/- 25% or 50% based on the values in the base case. By varying the values the 'best' and 'worst' case scenarios were examined. The sensitivity analysis appears appropriate based on the range of the value in the base case.

The sponsors state that "one-way sensitivity analysis is sufficient to explore the uncertainty around base case results", so that the probabilistic or two-way sensitivity analysis was not undertaken in the submission. The EAC agree that complex probabilistic sensitivity analysis may not have important added value in this case, given the relatively simple model structure and parameters involved, and the limitations of the available data.

4.8 Results of de novo cost analysis

4.8.1 Base case analysis results

Results from the sponsor's base case analysis are reported in Table 4.3 below. The EAC confirmed that the results reported in the submission match the output of the submitted models.

Table 4.3. Base case result

Clinical setting	Intervention	Mean cost per patient (£)
Unexpected difficult intubation in operating theatre	Ambu aScope	520
	Reusable scope	588
	Ambu aScope vs. reusable scope	-68
Unexpected difficult intubation in ICU	Ambu aScope	1,085
	Reusable scope	1,215
	Ambu aScope vs. reusable scope	-130

Dislodged tracheostomy	Ambu aScope	13,911
	Reusable scope	15,467
	Ambu aScope vs. reusable scope	-1,556

4.8.2 Sensitivity analysis results

The sponsor varied costs associated with reusable scope and hospitalisation, and also the rates of failure intubation and risk reduction for Ambu aScope in sensitivity analyses.

The findings were sensitive to the parameter changes in all three clinical settings. The Ambu aScope remained cost saving in scenarios specified in the sponsor submission, except in scenarios of long lifetime equipment or a substantially low equipment cost for the reusable scope. The EAC retested these sensitivity analyses, and confirmed that the results were consistent with those reported in the submission.

The EAC explored the sensitivity by increasing the number of procedures performed per annum from 150 to 200 to illustrate how the comparison of equipment and staff costs change, with a cut-point around 185 where the costs of the two approaches are roughly equal. As the number of procedures increases, the balance of costs increasingly favour reusable scopes (Table 4.4). However, the sponsor's model indicates that when other costs are taken into account the Ambu aScope2 remains cost saving, due to the assumption of availability reducing adverse outcomes.

Table 4.4 Sensitivity analysis associated with number of procedures with reusable scopes annually, with regards to equipment and staffing costs only

Number of procedures with reusable scope annually	Average cost of reusable scope (£)	Average cost of Ambu aScope (£)	Reusable scope vs. Ambu aScope (£)
150 (base case)	209	179	30
185	176	179	-3
200	165	179	-14

4.9 Subgroup analysis

No subgroup analysis was undertaken in the submission.

4.10 Model validation

The validation of the submitted models was not undertaken. The sponsors claimed that there is very limited information in the literature. They also stated that the model aimed to capture the costs and consequences of the Ambu aScope and reusable scope. They argued that the model was more likely to provide the details of cost analysis rather than cost-effectiveness analysis since there is very limited clinical evidence on the use of Ambu aScope in the specified setting at present.

4.11 Interpretation of economic evidence

The sponsor stated the results of economic analysis were broadly consistent with the existing evidence. They claimed their findings were consistent with the conclusion in the published study by Tvede et al. (2012). They also noted that existing analyses have not considered relevant clinical outcomes.

The EAC are concerned with the assumptions made in the model. Many exploratory assumptions were made regarding input parameters in the submission. The sensitivity analyses indicated that there was great uncertainty surrounding the results. More crucially the key input values that drive model outcomes are concerned with availability issues, and no evidence is provided for this assumption.

4.12 Additional work undertaken by the External Assessment Centre in relation to economic evidence

1. EAC has re-done the literature search using a broader range of terms (see Appendix 2) and identified 30 more papers. We have screened the abstracts and did not find any additional relevant papers.
2. EAC conducted a brief search of MEDLINE (Ovid) 1946 – June week 3 2012 for studies on the topic of delayed or failed intubation. This search located 258 references, and the search strategy is described in Appendix 1.
3. EAC reviewed the sponsor submitted model and did quality checking for its intended purpose, confirming that the model and the submission were consistent.
4. EAC suggested an alternative model structure (Figure 4.3), the purpose of which is illustrative only. It aims to capture the potential supply-chain failure problem where there is a delay in accessing reusable scopes but more readily

available Ambu aScope2s are at hand. It makes the assumption that single-use scopes overcome the supply chain problem but that a similar number of reusable scopes result in non-availability.

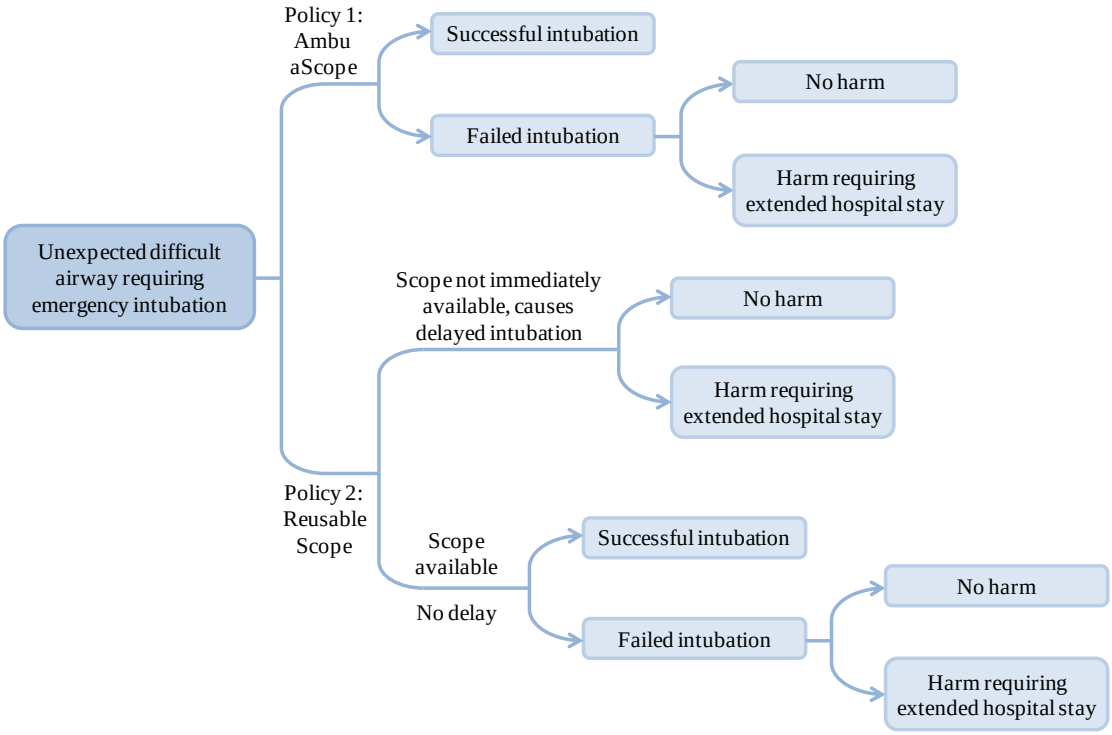
When a reusable scope is available, the rates of failure of intubation and of harm caused by the failure are the same for both settings. The latter assumption is broadly supported by the clinical evidence review (question1).

Although death and permanent brain damage are possible outcomes of failure of intubation, and are also extremely costly, the EAC found no evidence to permit estimation either of the likelihood of such outcomes or the proportion of these that might be avoided by more timely use of a scope to assist intubation. The implication is that such cases are very rare, and it is very rare for a person to suffer permanent damage from a failed intubation; measured in the tens of thousands.

The EAC did not locate any evidence differentiating between the use of fibrescopes for unexpected intubation difficulties and displaced tracheostomies, and accordingly these are treated together as ‘unexpected airway difficulty requiring emergency intubation’.

We assume in this model that Policy 1 (Ambu aScope2 – see Section 1.5) obviates the problem of non-availability, which is unlikely to be true, as discussed above.

Figure 4.3 Model of unexpected difficult airway-requiring intubation revised by EAC



5. EAC approached clinical advisers to estimate the proportion of cases where guided intubations are needed but a reusable scope is not immediately available.

6. EAC performed a basic calculation, based on our proposed model structure illustrated in Figure 4.3, and used the two input values obtained from experts' opinions: the rate of delayed intubations caused by non-availability of a reusable scopes, and the rate of harm of delayed/failed intubation in unexpected difficult intubation. Table 4.5 presents the input values used in this estimation.

   The model is for illustrative purposes only. It aimed to present the case that the difference in the care pathway between Ambu aScope2s and reusable scopes was a supply-chain failure problem, rather than of clinically important differences in effectiveness. However, there is no real evidence to inform such values and populating the model would only be an estimation. The EAC decided not to conduct detailed sensitivity analysis.

7. To illustrate the use of the model, consider the path from 'Unexpected difficult airway requiring emergency intubation' via Ambu aScope in an operating theatre (OT) setting. There is a device cost of £179. For a particular patient the probability of intubation failure in an OT setting is 0.0625, which incurs

further costs. The complementary probability (1–0.0625) is the probability of intubation success and there are assumed to be no further costs. The probability of harm resulting from failure is taken as 0.74 (from sponsor's submission) and the cost of this harm is estimated as 6.2 days at a cost of £1,321 per day (figures taken from sponsor's submission). The total expected cost is thus (179+(0.0625×0.74×6.2×1321)), which is equal to £558.

Table 4.5 Summary of values for parameters used in the model

Parameters	Value	Source
Reusable scope – cost per scope	£209	Sponsor's submission
Ambu aScope2 – cost per scope	£179	Sponsor's submission
Rate of failed intubation in unexpected difficult intubation patients: Operating Theatre setting – reusable scopes and Ambu aScope2	0.0625	Sponsor's submission
Rate of failed intubation in unexpected difficult intubation patients: ICU setting – reusable scopes and Ambu aScope2	0.166	Sponsor's submission
ICU length of stay – Failed intubation– reusable scopes and Ambu aScope2	6.2 days	Sponsor's submission
Rate of ICU admission or prolongation of stay – Failed intubation– reusable scopes and Ambu aScope2	0.74	Sponsor's submission
ICU – cost per day	£1,321	Sponsor's submission
Rate of delayed intubation in unexpected difficult intubation patients: Operating Theatre setting and ICU – reusable scopes	10%	Clinician expert opinion
Rate of harm requiring extended hospital stay in difficult intubation patients where intubation was delayed	50%	Clinician expert opinion

The results estimated from the EAC model were summarised in Table 4.6. The total cost per patient (for the avoidance of doubt, this relates only to a patient with an unexpected difficult airway requiring emergency intubation) for Ambu aScope2 and reusable scopes were £558 and £959 in operating theatre settings, and £1,185 and £1,524 in ICU settings respectively. In both clinical settings, use of the Ambu aScope2 was cost saving compared with reusable scopes. However, the results are based on expert opinion and the sponsor's assumptions for the rest of the parameters, implying some unquantifiable uncertainty.

Table 4.6 The base case result conducted by EAC

Clinical setting	Intervention	Mean cost per patient (£)
Unexpected difficult intubation in operating theatre	Ambu aScope2	558
	Reusable scope	959
	Ambu aScope2 vs. reusable scope	**-401**
Unexpected difficult intubation in ICU	Ambu aScope2	1,185
	Reusable scope	1,524
	Ambu aScope2 vs. reusable scope	**-339**

8. EAC suggested including a scenario where Ambu aScope is used in a complementary mode to reusable alternatives when reusable scopes are not immediately available in this setting.

4.13 Conclusions on the economic evidence

The EAC base case analysis (using expert opinion to parameterise the model, necessitated by extremely limited or missing clinical evidence) shows that the Ambu aScope 2 offers cost savings compared to multi-use scopes. Due to use of expert opinion there is unquantifiable uncertainty around the estimates. Sensitivity analysis shows that, if multi-use scopes were always readily available, the cost advantage of the Ambu aScope2 reduces with increasing instances of use and is reversed at around 185 uses per year (Table 4.4). In the sponsor analysis, the key potential benefit of Ambu aScope2 compared with its alternative was its immediate availability. However, there is no real evidence on how often this “supply chain” problem occurs and the extent to which it is mitigated by a policy for a switch from reusable to single-use scopes.

The safety of the patient with an unexpected airway difficulty requiring emergency scope-guided intubation might be improved by increased availability of reusable scopes or single-use scopes (for use only as required). For example, ICUs and operating theatres could be required to have a single-use scope ready for use at all times. This would not require replacing reusable scopes with single-use scopes, instead only that the single-use scope be on hand for occasions when a scope is required urgently, but a reusable scope is not available.

The costs and benefits of providing single-use scopes for unanticipated difficult airway management depend on the following factors:

a. The number of events (*n*) in which a reusable scope is not immediately available and a single-use scope would be used.

b. The proportion (*p*) of these cases in which the immediate availability of the single-use scope improves the health outcome.

c. The average value of the health outcome improvement (*v*) in these cases. (The best scenario is that all delayed cases due to unavailability of reusable scopes were avoided).

However, there is no evidence base from which to estimate these quantities.

If there is a real problem of delayed or failed intubation due to supply chain failure, then an alternative would be to purchase more reusable scopes. Again the key questions would then be:

1. How often the emergency scope(s) would be required.
2. How often emergency situations arise where, despite having the extra scope, no scope would be available.

This depends on the frequency of use of the emergency scope (in effect the distribution of emergencies over time). Even if this was known, costing this option might be difficult as procedures would have to be put into place to ensure that an emergency scope was prepared for use quickly after each previous use.

Therefore, the main issue is the immediate availability of scopes for emergency use in, for example, A&E, ICU and theatre. It could even be considered that a scope be a standard part of emergency equipment. However, in this case the economic comparison would be more complex, as the capital (purchase) cost of a single dedicated reusable scope would form an important part of costs if it was used infrequently. In this case, an estimation would need to be made as to the number of times the scope would be used to assist in difficult intubations or in checking and repositioning tracheostomies in a particular time period (such as one year).

5. Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

If the Ambu aScope is mainly used to complement the use of reusable scopes, the increased availability of single-use Ambu aScopes is unlikely to reduce the purchase and maintenance costs of reusable flexible optic scopes. The additional costs required by the use of Ambu aScopes depend on the frequency of cases with unanticipated difficult airways. This has not been considered in the sponsor submission, possibly due to a lack of data on this important variable.

6. Conclusions

The review does not suggest that the Ambu aScope2 should replace conventional devices on the ground that it is more effective. While the trials are inconclusive, the point estimate favours conventional equipment. Moreover, conventional equipment provides better visualisation of the anatomy and allows for a wider range of clinical procedures and techniques. Taken in the round this would suggest that, if anything, conventional equipment is more effective. Moreover, there is no strong argument to switch from conventional device to the Ambu aScope2 on the grounds of lower costs (on an assumption of equivalence for effectiveness). The cost differences appear small and they are certainly unstable (perhaps even ephemeral).

Attention therefore turns to issues of the supply chain on which availability depends. Here we encounter a topic even less informed by evidence. We do not know how big the problem of unavailable instruments is. More important still, we are presented with no real evidence that providing single-use instruments will overcome or mitigate the problem, given the same expenditure or provision of the same total number of scopes per patient. This could not be studied by any realistic trial, which would have to be a cluster study. Detailed field studies of the supply chain might help, however. In the meantime, the option of a policy where single-use scopes in medium risk environments complements reusable devices in high-risk environments may be sensible.

7. Implications for research

The literature search presented in the Sponsor's report and commented upon here could be updated at a later date to include studies that have been identified but not reported. Full results from two studies (Lenhardt et al. 2011; Kristensen et al. 2011) were not published. Two other RCTs were in progress and not published. These studies address failure of intubation in difficult airways and safety issues with Ambu aScope compared with conventional reusable scopes. The EAC identified potentially relevant publications concerning safety, and a full systematic review of safety issues associated with delay or failure of intubation could be conducted.

The EAC has proposed an alternative economic model addressing the use of Ambu aScope in a complementary manner to mitigate risks when reusable scopes are not available. This could be implemented, but would still be hard to populate. Primary research into the numbers, locations of and need for intubating fibrescopes for emergency and "difficult airway" situations in NHS settings would almost certainly be required to inform the model. Further research, which might be both secondary and primary, might be needed to inform parameters around risks attached to scope unavailability.

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Appendix 1. EAC Search Strategy for Delayed or Failed Intubation

Search Strategy conducted in Ovid MEDLINE® 1946 to June week 3 2012

Search	String	Results
#1	(delay$ adj intubation).mp.	18
#2	(failure adj intub$).mp.	10
#3	failed intubation.mp.	230
#4	or/**1-3**	258

Appendix 2. EAC Economic Search Strategy

Search Strategy conducted in Ovid MEDLINE® 1946 to June week 3 2012

Search	String	Results
#1	(unexpect$ or expect$ or anticipat$ or unanticipat$ or emergenc$ or predict$ or unpredict$ or difficult or closed or obstruct$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1 788 457
#2	(airway$ or airway*-management or trache$ or dilat$ or PDT or intubat$ or translaryngeal or laryngeal or tracheal or endotrach$ or emergency-resuscitation or foreign-body).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	393 652
#3	(ascope$ or ambu or ambuscope).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	186
#4	(scope$ or fibre$ or video$ or endoscope$ or bronchoscope$ or laryngoscope$ or sheath$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	212 480
#5	**1** and **2** and **3** and **4**	8
#6	**2** and **4**	14 511
#7	cost*.mp.	359 062
#8	**6** and **7**	279
#9	economics/	26 328
#10	exp "costs and cost analysis"/	40 863
#11	cost of illness/	15 166
#12	exp health care costs/	40 863
#13	economic value of life/	5 222
#14	exp economics medical/	13 284
#15	exp economics hospital/	17 982
#16	economics pharmaceutical/	2 342
#17	exp "fees and charges"/	25 870
#18	(econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.	372 398
#19	(expenditure$ not energy).tw.	15 175
#20	(value adj1 money).tw.	18
#21	budget$.tw.	15 400
#22	or/**9-21**	501 723
#23	**6** and **22**	295
#24	**23** not **8**	30
#25	**8** not **23**	14

The EAC ran a broader economic filter (one created by CRD) to expand the terms for costs, and without a date or language limit in place – search #24, which returned 30 references the sponsor's search did not find. However, search #25 returned 14 references that the sponsor's search did find, but search #24 did not.

Appendix 3. NICE EAC Correspondence

National Institute for Health and Clinical Excellence

External Assessment Centre correspondence

MT158 Ambu aScope for difficult and unexpected airways management

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need 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 made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Relative effectiveness of Ambu aScope vs. Standard instruments. For the first set of questions, our impression from the literature is that the Ambu aScope2 is a little harder to use than standard equipment. On average it takes longer to complete intubation when an Ambu aScope2 is used to assist the procedure than when standard devices are used. Is this correct in your view?	**Expert 1:** No. It feels 'cheaper' but it works just as well. The range of movement is similar and the video screen is good enough. Its advantage is portability without a large 'stack system' to display the images. The images are of course not as good as the expensive alternatives but they are certainly good enough. **Expert 2:** The time differences in both studies were small. It is difficult to make an assertion based on the published evidence that the time difference was clinically significant. Also it is not clear whether the Ambu aScope or the Ambu aScope2 was being evaluated and this may have had a significant bearing on the time to intubation as the slow	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic model

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		responsiveness of the screen was one of the problems with the original model. It is certainly true that the aScope2 is a little more awkward to manoeuvre than its reusable counterparts but as the collision study showed there was no difference. **Expert 3:** I am of the view that the Ambu aScope2 should not be considered as a direct comparator and alternative for standard video bronchoscopes. It is an alternative when standard scopes are not immediately available, for example in an emergency situation. I think the concept of it being harder to use is a difficult area as the reasons are multifactorial, including familiarity with the device. However, I feel it is not as versatile an instrument or as robust as a standard scope and therefore I could anticipate that	

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		it may take a little longer to complete an intubation. I do not have direct personal experience to support this. **Expert 4:** You really need to define what you mean by standard equipment. If you are talking about other flexible endoscopes particularly the reusable devices which most commonly for anaesthetics are fiberoptic based, then answer is no aScope is not harder but easier (can expand if required). If you are comparing with a standard retractor type laryngoscope (essentially a bent spoon with a light!) then the answer is a resounding yes, but that is almost a tool aimed at a different task.	
	Question to Expert Advisors (Consultant	**Expert 1:** It depends what you assessing. Ambu	Comments taken

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	anaesthetists / Consultant in Respiratory & Critical Care Medicine): Is it unlikely that the Ambu aScope2 is better/more effective than standard alternatives? Indeed no claim of superiority is made. Can you confirm our impression?	aScope has poorer optics and no suction but will achieve virtually all of what an expensive alternative will. If you have a £20k scope in the washer 10 minutes away and you need a scope in an emergency, I would consider then that the aScope is 'more effective'. However, in an elective situation, where aScope and an expensive re-useable scope were available to me, I would choose the expensive one usually. **Expert 2:** I would agree, its superiority lies in its disposable nature making it ideal for infected cases. The fact that it comes in a sterile package also means that it could be made rapidly available in areas without storage and cleaning facilities.	into account in the EAC's assessment of the clinical effectiveness data and the economic model

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		Also its rapid assembly time is also a potential attraction Its major drawbacks are i) the fact that an Aintree catheter cannot be placed over it [I have discussed this feature with one of the authors of the NAP4 report who underlined the fact that any scope to be used as a rescue device should be compatible with an Aintree catheter and facilitate fibreoptic intubation via a supraglottic airway- ii)the absence of a working channel for the placement of guidewires/ epidural catheters etc – The Aintree issue is Very Important [I do not refer to the working channel of any fibreoptic laryngoscope as appropriate for suction, so	

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		this is not an issue with the aScope2] **Expert 3:** Yes, I would agree with this view. It is has distinct advantages in terms of immediate availability in the management of the emergency airway. I do not believe it is superior to standard scopes. **Expert 4:** This question would suggest you are comparing with, at least now, reusable endoscopes. If that is so then answer is aScope can be better depending on what generation of flexible endoscope is used in that institution and how well it is maintained. E.g. Elderly fiberoptic device with slack control lines on the control lever and or multiple broken fibres or poor light source or poor picture	

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		adjustment (all very common scenarios) will be much inferior to aScope.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Delay in inserting an endotracheal tube is a reasonable surrogate for overall safety; while in an individual case a delay of, say, 10 seconds may not be important but in some cases a delay might be critical. Could you comment on this?	**Expert 1:** To my knowledge, the published data on the use of this scope is that it is comparable in performing intubations in terms of time. 10 seconds is unlikely to be critical and is probably more than compensated by aScope's immediate availability (compared to getting a reusable scope out of a drying cabinet). **Expert 2:** This is a difficult and complex question, and cannot be answered in the same was as when dealing with conventional laryngoscopes The operator must be familiar with the equipment and the technique.	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic model

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		The Ascope2 is quick to set up, but people must be familiar with the technique of using it. In an awake patient a delay in the placement of an endotracheal tube is not an issue, as the patient is awake and self oxygenating. It is the adequacy of topicalisation that is important in terms of patient tolerance and this is not a feature that can be attributed to the scope. An asleep fibreoptic intubation should only be attempted when the patient can be adequately oxygenated by an alternative means- or the failed intubation drill should be in use. Here there are some questions to be answered Because the aScope2 cannot be used with an Aintree catheter, a low-skill fibroptic intubation that	

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		all anaesthetists are expected to learn to do during their training is not possible. However, the ready availability (assumed) of the aScope2 may allow the trachea to be intubated in a more timely fashion than having to delay will a conventional reusable scope is sourced (cleaned in certain circumstances) and assembled- The Vijayakumar study showed a clear learning curve with both devices- this was clearly learning the scenario- but the difference between the two devices also narrowed (extrapolation is difficult here as this was not a primary outcome measure) **Expert 3:** I would agree that immediate availability of equipment to support a difficult airway and	

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		avoidance of delay is a surrogate to support overall patient safety. A delay in inserting an endotracheal tube could be critical in some situations. Particularly relevant would be the acutely unwell or emergency patient, for example in an intensive care environment. It is less likely to be as much of a problem in an elective situation with a well pre-oxygenated patient, for example in a intubation prior to a planned operation. Underlying cardiorespiratory disease may have an impact on this situation, by increasing the risk of hypoxia caused by a delay to intubation. The risks would be higher in an acutely unwell patient in an emergency situation who is dependent on high concentration of oxygen. A delay of up to 10 seconds could be of relevance and result in additional morbidity related to hypoxia.	

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		Expert 4: Disagree that "*inserting an endotracheal tube is a reasonable surrogate for overall safety*," as this is a poor surrogate for safety, though often used. Delays of 10 seconds are probably no significance. "Delay to insertion" is often used as a indicator of ease of use of a device, rather than safety. In truth it's not a delay, but duration of procedure. Depends what papers you are reading.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Logistical / supply chain issues The second set of questions deal with the claim	**Expert 1:** This depends on your hospital's infrastructure and workload. We have over 120 scopes, and use 4 for our 23 bedded ICU. There is always one available, even if we use 2 out of hours. We had to buy 2 extras though when we went to centralised decontamination to ensure these were	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic

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	that conventional scopes are sometimes not available. This may arise if they have been recently deployed and are away for cleaning or if they have not been deployed in a specific location. Since the industry case is based on this scenario we need to know more about this issue. How often does the situation arise that no scope is available when the need arises. How does this vary across locations within a hospital? There may be no data on this rather specific question but some sort of expert impression of the size of the problem would be most helpful. Even anecdote would be useful. For instance have you heard of patient's coming to harm because a scope was not available?	always available. A smaller unit with only 1 or 2 scopes may be harder to have 1 available always. Most cleaned scopes are kept in expensive drying cabinets to keep scopes clean for 72 hours. They need monitoring and then re-washing after this (infrastructure required to do this). It is not inconceivable that if you use a scope at midnight on Saturday and then need another immediately for something else, you may have no more scopes available in your area. The cost of providing a few scopes, the cabinet and the people to monitor and decontaminate these scopes is large. If the scopes are there for occasional emergency use (e.g. on an ENT ward or resp ward) then the aScope is a very attractive alternative. Our 2009 and 2010 critical incident reviews included detailed cases of harm	model

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		occurring due to non availability of equipment. I have attached the 2010 paper. We did not report the specific number of scopes here. **Expert 2:** This again is a difficult question. NAP4 [5] is clear that we do not do enough fibreoptic intubations. I have discussed this with a NAP4 editor and he has confirmed that cases were reported to NAP4 where fibreoptic equipment was not available when needed. This was most notable in reports from ICU and the ED. Lack of availability was reported from operating theatres also but it was not a widespread feature. We also know that scope availability varies- in a survey we did in 2010 in England Wales and	

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		Northern Ireland, We obtained data from 127 hospitals (53%). Access to FOI equipment was possible in 127 sites (100%), with the mean scope to theatre ratio being 0.4, range 0.09 to 1.0 [6]. In a hospital where there is only one scope, should it become damaged then alternative means of performing a fibreoptic intubation have to be found- Even in a hospital with many scopes, should the cleaning system develop a fault then all of its reusable scopes are out of commission, unless they have been appropriately stored in a HEPA Cabinet- which is itself a major financial outlay particularly if the number of scopes maintained by an organisation is small. I have certainly been told of difficulty accessing a	

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		fibreoptic scope by several individuals because it has to be transported between sites or borrowed from another hospital. I have asked some of my colleagues whether they have actually heard of a specific case of harm because a fibreoptic scope was temporarily unavailable. Another point to consider is the issues surrounding trace-ability and loan scopes- where a company may previously have loaned a replacement scope, now unless they can meet strict trace-ability the hospital may not be able to accept a loan device **Expert 3:** I do not have specific numbers to inform this question but am aware of situations where there	

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		has been a delay in getting hold of a “clean” standard scope quickly. Cases of clinical harm do not come to mind immediately. The issues here relate to the time taken to clean a standard scope or accessing a clean standard scope out of hours in theatre or intensive care. Many hospitals will now have a system of centralised sterilisation of endoscope equipment and therefore do not have the standard scopes immediately available in the place they need to use them. This is based on robust infection control and prevention procedures. They are often packaged, sterilised and stored remotely from the clinical environment. The advantage of the Ambu aScope is its immediate availability in the location it is required, for example in the case of a dislodged tracheostomy in an ICU patient. Standard	

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		scopes usually have a separate “stack” for the video equipment which are cumbersome systems to be moved to the bedside in an emergency airway situation compared with the Ambu aScope. **Expert 4:** “*How often does the situation arise*…?” - Can not answer this, at one time this was common, but now probably few hospitals are without an endoscope for airway use (not sure here about small private hospitals and clinics etc). **It’s probably more important to realise that flexible endoscopes (FE) may be available in theory and yet their use untenable** because they are far away, poorly maintained, unfamiliar to staff and seen consequently as a last resort rather than a ready and easy tool. **It may be reasonable to contend that**	

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		any operating theatre suite which has only one reusable FE should carry some aScopes for when that device is being processed or repaired or even in use. "*How does this vary…?*" – Hugely. Operating theatres in UK DGH are rarely without at least one FE but obstetric theatres, A+E units, Intensive Care units likely to not have. "…expert impression of the size of the problem…?" – NAP 4 audit looking at theoretically all instances of airway harm in UK has particular references to FE use for airway management. If you are not familiar with this document, may I suggest its perusal or let me know if you need some parts interpreted. For sure FE not used frequently where it should have been, the reasons for this may be to do with general	

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		availability and ease of set up.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Given that sooner or later the situation will arise where a scope is not available when needed, the sponsor argues that Ambu aScope's should be available in locations where *unexpected* difficulties may arise and that standard instruments would not be available there?	**Expert 1:** Where you are expecting difficulties (eg an anaesthetic list with a difficult elective case) one would usually plan to have a high end scope electively available. For unplanned emergencies, a high end scope may be immediately available (usually in a nearby drying cabinet, eg for an ICU or theatre suite) or the aScope may be useful in speeding up the availability issue. For remote sites or wards which do not have the infrastructure to buy the scopes and decontamination facilities, the aScope offers a rapid and effective solution. **Expert 2:** Within the terms provided, the question is challenging, so I must apologise if I stray outside	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic model

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		them. The primary purpose of a fibreoptic scope is to facilitate tracheal intubation. In itself it does nothing to oxygenate the patient. The properties of the scope are probably much less important (within certain limits) than the quality of the operator (vide supra). It is certainly true to say that there are many places within a hospital where I would not expect to find a reusable fibrescope unless I had made specific provision for one to be available there. The Ascope2 offers a readily available, rapidly ready to use fibrescope, and if practitioners are experienced in their use then it may be quicker to use it in departments out with a main theatre suite- e.g. to perform a tracheostomy on ICU or to do a	

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		fibreoptic intubation in a distant site (intensive care or the emergency department). Access to a low cost scope in these areas may overcome the lack of availability, but only if it is compatible with the guidelines. The Ascope2 is limited in the unanticipated difficulty because of the issues with an Aintree catheter- although it could be used effectively to place an endotracheal tube by a skilled operator in an unanticipated difficult airway situation- and in a remote site where there would have to be a delay in obtaining the reusable equipment a rapidly available device may be best Importantly, in unanticipated difficulty the primary aim is oxygenation rather than intubation and the	

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		Ascope2 does not change that. **Expert 3:** I would agree with this view, in environments such as intensive care and theatre recovery areas. **Expert 4:** Probably not an unreasonable comment, although potentially self defeating: if planning to stock areas where an unexpected difficulty may arise then it is not strictly unexpected and perhaps ordinary FE should be available. More generally: from the outset of this NICE evaluation I have repeatedly stated that if there is value in aScope it lies in its making FE available at minimal start up and maintenance costs compared with the reusable	

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		devices. This has potentially the effect that it can make reasonable the aim of having FE so widely available that its use as a technique of airway management becomes extremely commonplace and hence is used earlier and more often. This would match the recommendations of NAP4. The obsession with directing the NICE evaluation / investigation at "unexpected" difficulties is a distraction and complication in an otherwise useful exercise.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Are there any clinical arguments for preferring	**Expert 1**: In an emergency, if I was offered an aScope AND a conventional high end scope simultaneously, I would choose the high end scope. In my view, the advantage of the aScope is its immediate availability.	Comments taken into account in the EAC's assessment of the clinical effectiveness data

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	the Ambu aScope in this situation? To put this another way, if not costs were equal, then would Ambu aScope2s be preferable? We think the answer is 'no', given the above, but would like your opinion.	**Expert 2:** If costs were equal, the benefit of the Ascope2 is its rapid assembly and availability (plug and play, no white balance required). It also has certain advantages in the ICU where the scope cannot be damaged (like a reusable scope) during the performance of a percutaneous tracheostomy **Expert 3:** If a standard video scope was immediately available in an emergency situation I would choose it over the Ambu aScope. I do not think the Ambu aScope would be preferable compared with a standard scope given a level playing field of access to the equipment.	and the economic model

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		Expert 4: There is no reason to prefer the aScope over a well maintained high end reusable FE which these days is likely to have a video chip at the tip and to not rely on fiberoptics for image transmission. These are relatively easy to manage in terms of connecting up to a monitor and generating an image. The picture quality from them would be better and the handling of the device better, however again ready availability is an issue.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Does the standard scope have any other uses	**Expert 1:** Better optics and suction are usual advantages. The standard scopes are usually thinner and can be used with alternative difficult intubation devices such as the Aintree catheter. The current aScope is too wide for this use.	Comments taken into account in the EAC's assessment of the clinical effectiveness data

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	apart from facilitating difficult intubation and dislodged tracheostomy?	**Expert 2:** This is where the fibreoptic laryngoscope differs from a fibreoptic bronchoscope- Uses are essentially the placement of a tracheal tube or tracheostomy tube and the replacement of same, but I have also used the devices to inspect the airway and check tube placement. Nasendoscopy and tracheoscopy are specifically recommended in NAP4. The latter may be required urgently to confirm tracheal occlusion by blood clot in the absence of detectable CO2. **Expert 3:** The standard video bronchoscopes are diagnostic and therapeutic instruments. They allow inspection of the airways for mucosal and structural	and the economic model

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		abnormalities. They allow diagnostic sampling of the airways in terms of bronchial biopsies, bronchial brushing, washing and bronchoalveolar lavage. This is an essential component particular for the patient intubated and ventilated on an intensive care unit. The standard video bronchoscopes allow suction of the airways with an adequate suction channel to remove secretions and mucus plugs. **Expert 4:** Yes, can be used for assisting percutaneous tracheostomy and diagnostic and or therapeutic bronchoscopy, including bronchial lavage and biopsy. (note that the devices aimed at working in the bronchi have a much larger external diameter to accommodate the larger working channel and they have a more flexible section above	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		the steerable tip, and are hence less ideal for tracheal intubation).	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Are there any particular difficulties in cleaning or sterilising standard scopes?	**Expert 1:** As alluded to above. It takes 1 hour minimum and up to 4 hours for a scope to be taken to the decontamination suite, cleaned, packed up and returned to our local drying cabinet. This service is available in our Trust from 9-6 weekdays and 9-3 weekends. If we use a scope at 3pm on a Saturday, we won't get it back until 11am Sunday for example. This is why we have spares (cost around £10k each). If we use 2 scopes out of hours, we have to then borrow from nearby theatres etc which adds delays in emergency. We have also had a recent incident where the wrong scope was bought from the cabinet in an emergency (a bronchoscope which	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic model

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		was too big for intubation, followed by a battery powered scope where the battery was missing. The scope we needed had a small mains powered light source which was eventually located, but we used the aScope in the meantime). These are local examples but I think our ICU is representative of the problems associated with scope availability. **Expert 2:** Standard scopes must be leak tested prior to cleaning, as cleaning a damaged scope will cause further damage. Unless kept appropriately (HEPA Cabinet) a 'clean scope' will be officially unclean after 4 hours whether used or not. Repeated cleaning of reusable scopes will shorten	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		their working lifespan There are infection control issues over prion diseases Regular cleaning of scopes on Difficult Airway Trolleys is therefore necessary even if they are not used. It would be very convenient and probably quite cost effective if we could leave a packaged sterile disposable scope on such a trolley- however such a scope must be compatible with the guidelines. **Expert 3:** I do not believe there are any particular difficulties in cleaning or sterilising standard scopes. As described above it is access to a clean scope particularly out of hours. Because of requiring robust infection control and prevention procedures most	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		standard scopes will be cleaned and sterilised in a central cleaning unit for all endoscope equipment. There is usually a reasonable turnaround time of a less than an hour at the point it is required within working hours. Out of hours a standard scope is usually left packaged sterilised and stored in a central store to be collected when required. There would therefore be a potential delay in an emergency situation by not having access to a clean scope in an instant for an emergency airway problem. In all other less urgent situations there is usually time to wait for a standard scope to be collected. **Expert 4:** Just expense, equipment and staff. When used in patients with possible transmissible	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		encephalopathies (e.g. nVCJD) they must be quarantined until diagnosis is certain and then destroyed.	
	Question to Expert Advisors (Consultant anaesthetists / Consultant in Respiratory & Critical Care Medicine): Are there any material differences between the standard scopes deployed in this country? Is there any particular type that is particularly suitable/unsuitable in use?	**Expert 1:** Yes. Features that vary include: Size Suction Extra working channel (unusual in these small scopes) Optical quality Eye-piece, connected to a 'stack' (lightsource and monitor) or a small screen attached to the 'scope itself Durability – some makes are notoriously easy to damage	Comments taken into account in the EAC's assessment of the clinical effectiveness data and the economic model

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		Support from the company – eg if it breaks, how quickly can we get a replacement / repair. These are delicate and are used (with tracheostomy placement at least) in the vicinity of needles and devices that can puncture or injure it. **Expert 2:** Subtle differences exist but scopes compatible and between video systems and glass fibrescopes however in a recent procurement exercise that I was involved in we specifically rejected the reusable scope that could not be used in conjunction with an Aintree catheter even though the image quality was better. **Expert 3:** Most modern standard scopes are video-	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		scopes with excellent image resolution. They vary in terms of size (diameter) and channel size. This relates to their diagnostic and therapeutic capabilities. In general the thinner scopes allow inspection of more distal airways whereas the larger the channel size allows for improved suction and therapeutic sampling such as larger biopsy forceps. There are still some scopes in use which are fibre-optic and require the operator to look down the scope to see the image or have a camera adaptor to allow projection t a monitor. In the former situation it is not recommended for the operators head to be directly over to avoid splashing of respiratory secretions into the eyes. The use of camera adaptors to slave an image to a monitor results in degradation of the image quality. The fibre-optic	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
		scopes therefore should no longer be used. The video monitor attached to the Ambu a Scope provides an excellent image and does not require the user to “look down” the scope. **Expert 4:** Devices may be fiberoptic based or video chip based, the latter are newer better and more expensive currently. Otherwise little to choose.	
	Question to Sponsor: Question 1: Report Section 4.5 (page 30) mentioned 1600 units of Ambu aScope have been purchased in England since late 2009. **How many units have been sold worldwide?**	**Sponsor:** Please find the overview of our global sales figures for aScope 1 and aScope 2 enclosed (See Appendix 6). It is broken down in our business regions as well, and based on unit sales.	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	Question to Sponsor: Question 2: Literature search strategy seems okay, but it is still unclear whether all unpublished and ongoing studies have been identified. Our rapid review has identified one trial and two abstracts which were not included in the submission. “Randomised controlled trial comparing the Ambu aScope with conventional fibreoptic bronchoscope in asleep orotracheal intubation of adult patients undergoing general anaesthesia (ACTRN12611001235998)”. The technology is new and most relevant studies may be sponsored or supported by Ambu Ltd. **Can Ambu Ltd please provide us with a**	**Sponsor:** The mentioned trial refers to the randomised controlled trial (ACTRN12611001235998), comparing the Ambu aScope with conventional fibreoptic bronchoscope in asleep orotracheal intubation of adult patients undergoing general anaesthesia, as listed on Australian New Zealand Clinical Trial Registry (ANZCTR; http://www.anzctr.org.au/trial_view.aspx?id=347774). At the time of the last update in February 2012, the stated date of first participant enrolment was 1st December 2011; however, the recruitment is still not initiated. Therefore, no data are available. Ambu A/S, Denmark, is a secondary sponsor of this study.	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	complete list of all published, unpublished and ongoing studies of aScope or aScope2 that they have supported or sponsored.	After having two abstracts handed out at a personal meeting June 15th and sought the cause for not having informed about these publications, we want to clarify that the two abstracts refer to articles by Scutt et al. (Anaesthesia. 2011;66(4):293-9) and Piepho et al. (Anaesthesia. 2010;65(8):820-5) that are included in the submission (See Appendix 4). Since the technology is new, independent investigators do initiate studies without our knowledge; thus, there may appear studies we are not aware of. The list of studies presented in the updated overview, represent to our knowledge, all the studies performed and on-going with Ambu aScope.	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	Question to Sponsor: The submission identified “six randomised studies and five observational studies”. However, Kumar 2011 and Vijayakumar 2011 reported data from the same study. It is essential that the number of “studies” should not be confused with the number of “publications”. **A check of duplicates and multiple publications of the relevant studies should be conducted.**	**Sponsor:** The two publications, Kumar 2011 (abstract) and Vijayakumar 2011 (full article), do indeed report data from the same randomised crossover study. We are sorry about this mistake. We have checked the rest of the data and have also been informed of two studies “Evaluating the Ambu aScope and alternative approach to endoscopic monitoring during percutaneous dilatational tracheostomy” by Austin and “First experience with the single-use Ambu aScope for fibreoptical monitoring in percutaneous dilatation tracheostomy” by Gernoth sharing some data from the same patients. However, the Austin study has extended the trial with a larger number of cases and endpoints. Additional duplicates/multiple publications have not been identified.	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	Question to Sponsor: Lenhardt 2011 is the largest study of identified studies that used aScope or aScope2 in real patients with difficult airways. The number of patients used aScope in Lenhardt 2011 (n=70) was much greater than the total number of patients in all other studies (n=43). However, results of Lenhardt 2011 are only reported in an Abstract (plus its protocol). Data reported in the abstract was very limited and no mention of safety and adverse effects. It seems that the Lenhardt study has been completed sometime ago and the internal report has been prepared. It is important for us to have full data from this	**Sponsor:** Dr. Lenhardt is not interested at the moment to share the raw data of the study due to copyright issues, since he is in the process of submitting the publication to a peer-reviewed journal (Please see our correspondence with Dr. Lenhardt in Appendix 8). Correspondence is initiated in order to obtain Dr. Lenhardt's consent to be contacted.	

Submission Document Section/Sub-section number	Question / Request Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
	study. **Can Ambu Ltd please provide us with the full report of Lenhardt et al. 2011 study (published or unpublished, as for the Kristensen study)?**		
	Question to Sponsor: Can Ambu Ltd please provide us with the full data on Vincent et al. 2011 (8 patients included)?	**Sponsor:** This is an independent study, and Dr Ahmed, the contact person of the study, has not responded to our request to the full data set (see Appendix 9).	

Please see Appendix 3.1 for additional comments from Expert 2.

Appendix 3.1 Additional comments from Expert 2

Piepho, Werner and Noppens:[1]
1) It is not clear whether it the aScope or the aScope2 that is being evaluated in this article, although the acceptance date of April 2010 and the use lief of 30minutes make it more likely to be the aScope
2) Their choice of a size 8.0 tube in a mannequin is interesting and may have added unduly to the difficulty
3) One of the key differences between the aScope and the aScope2 is the response time on the monitor- one wonders if the slower time with the aScope was at least in part due to the slow response time of the aScope- I have no absolute data for this
4) The failure rates in the diffficult scenario are difficult to understand, this was a mannequin study, the operators have all reported having done a large number of fibreoptic intubations previously and yet they even fail with the reusable scope...
5) small studies like this must be considered in the light of Pandit's editorial [2]

Summary of this study: Small time difference in mannequins which is unlikely to be clinically relevant, identified known features of the scope, some of which - image response time and secretions on the lens may have been corrected for by the aScope2

Vijayakumar, Clarke Wilkes et al [3]
Again, given an abstract of this work was presented in September 2010, unclear whether Ambu aScope or aScope2 being discussed- but again the discussion of a limited chip time to 30 minutes makes the aScope more likely

The correspondence generated by this article merits consideration- to show the present variation in opinion [4]

Although both studies show a time difference between the two scopes, it would not appear to be terribly clinically significant- only 5 real patients were included and their intubations were not timed.

The important features when doing an awake fibreoptic intubation are
1) Patient Preparedness (adequacy of topcialisation)
2) Skilled assistance
3) View
4) Operator skill
5) Attributes of the scope

What would appear to be missing for the Ascope2 is a large patient series in the literature from which conclusions might be drawn.

References

1. Piepho, T., et al. (2010). Anaesthesia; 65: 820-825. doi: 10.1111/j.1365-2044.2010.06406.x.
2. Pandit, J. J. (2012). Anaesthesia; 67: 578–583. doi: 10.1111/j.1365-2044.2012.07155.x.
3. Vijayakumar, M. (2011). Anaesthesia; 66: 689–693. doi: 10.1111/j.1365-2044.2011.06761.x.
4. Anaesthesia. (2011). Comparison of Ambu aScope and Olympus re-usable fibrescope: Responses. Available at: http://www.respond2articles.com/ANA/forums/thread/902.aspx?vol=66&iss=8&art=320772 (accessed 19th July 2012).
5. 4th National Audit Project of the Royal College of Anaesthetists and The Difficult Airway Society. (2011). Major complications of airway management in the United Kingdom. Report and findings, March 2011. Cook, T.M., et al. (editors). Available at: http://www.rcoa.ac.uk/node/4211 (accessed 19th July 2012).
6. Jeffrey, A. S., et al. (2011). European Journal of Anaesthesia; 28: P232P.

Appendix 4 List of studies

Remark: aScope = aScope first version

Title	Sponsored by AMBU	Published	Device
Comparison of the single-use Ambu aScope2 versus the fibreoptic bronchoscope for tracheal intubation in patients with cervical spine immobilization 2012 Schoettker, P. et al ESA 2012, Paris	No	Poster presented. Abstract published on the Proceedings of ESA 2012. Please refer to Identifier: NCT01467739, p. 30 in the clinical submission	aScope2
The Ambu aScope: a New Disposable Flexible Video Laryngoscope 2011 Schirin M. Missaghi, MD, Klaus Krasser, MD, and Ernst Zadrobilek, MD Internet Journal of Airway Management	No	Yes,	aScope
Fiberscope Versus Single Use Ambu aScope Bronchoscope For Control of Double-lumen Tubes and Bronchial Sutures 2011 C. Charles, W. Schmidt, P. Diemunsch ASA Chicago 2011.	Yes, provided aScopes	Poster presented. Abstract published on the Proceedings of ASA 2011.	aScope

Feasibility of a combined use of a video-laryngoscope with a novel flexible video-stylet for predicted difficult intubation 2011 Lenhardt, R. et al ASA Chicago 2011	Yes, provided aScopes	Poster presented. Abstract published on the Proceedings of ASA 2011., Manuscript including full data set is in preparation. Please refer to study of same title.	aScope
Evaluation of aScope2 in eight patients with anticipated difficult airways having awake fibre-optic intubations 2011 Vincent, V., Raval, M., Ong, C., Ahmad, I., DAS 2011	No	Poster presented, Abstract published on the Proceedings of DAS 2011. Manuscript in preparation. Please refer to correspondence attached in email with dr. Ahmad	aScope2
Evaluation of a single-use intubating videoscope (Ambu aScope ™) in three airway training manikins for oral intubation, nasal intubation and intubation via three supraglottic airway devices 2011 Scutt S, Clark N, Cook TM, Smith C, Christmas T, Coppel L, Crewdson K., Anaesthesia. 2011 Apr;66(4):293-9.	Yes, provided aScopes	Yes	aScope
Comparison of the manoeuvrability and ease of use of the Ambu aScope and Olympus re-usable fibrescope in a manikin 2011 Vijayakumar M, Clarke A, Wilkes AR, Goodwin N, Hodzovic	Yes, provided aScopes	Yes	aScope

I., Anaesthesia. 2011 Aug;66(8):689-93.			
The single-use endoscope aScope™ for fibreoptical monitoring in percutaneous dilatational tracheostomy: a feasibility study 2011 Perbet, S., Jabaudon, M., Cayot-Constantin, S., Guerin, R., Chartier, C., Constantin, JM., Bazin, JE., ESICM Berlin 2011	Yes, provided aScopes	Poster presented. Abstract published on the Proceedings of ESICM 2011.	aScope
The use of the Ambu Aura-i SupraGlottic airway in an iSGA-first rescue strategy 2011 Laursen, S., Samsøe Jensen, F., Kristiansen, A., Mazzaro, N., ASA 2011	Yes, provided aScopes	Poster presented. Abstract published on the Proceedings of ASA 2011.	aScope
Preliminary Evaluation of Ambu aScope 2 for Endoscopic Guidance During Percutaneous Dilatational Tracheostomy 2011 Jamadarkhana,S.,Mallick, A., Bodenham, A., ICS 2011	No	Poster presented. Abstract published on the Proceedings of ICS 2011	aScope2
Evaluating the Ambu aScope an alternative approach to endoscopic monitoring during percutaneous dilational tracheostomy 2011 Austin, P., Crawley, S., Christie, S., Cole, SJ. DAS 2011	Yes	Poster presented. Abstract published on the Proceedings of DAS 2011. Shares some of the data with the Gernoth study.	aScope

Evaluation of the Ambu aScope, a new single-use flexible videoscope 2011 Kumar, MV, Clarke, A., Wilkes, AR., Goodwin, N., Hodzovic, I., Anaesthesia. 2011 Aug;66(8):689-93.	No	The article is based on the same study as the article "*Comparison of the maneuverability and ease of use of the Ambu aScope and Olympus re-usable fibrescope in a manikin" by* Vijayakumar.	aScope
The videolaryngoscope Airwayscope makes the bronchial aScope videoscopy easier. 2010 SAUMANDE, B., WOLTER, J., SEGURA, P., POTTECHER, T.,DIEMUNSCH, P., ASA 2010	No	Abstract published on the Proceedings of ASA 2010	aScope
Interet du aScope pour la mise en place d'une sonde d'intubation selective a double lumiere 2010 Seramondi, R. , Roze, H., Germain, A., Perrier, V., Gallon, P., Regnier, P., Ouattara, A., Janvier, G., SFAR 2010	Yes, provided aScopes	Poster presented. Abstract published on the Proceedings of SFAR 2010	aScope
First experiences with the single-use Ambu aScope for fibreoptical monitoring in percutaneous dilatation tracheostomy 2010 Gernoth, C., Genzwuerker, H.V,ESA 2010	Yes, provided aScopes	Poster presented. Shares some of the data with the Austin study.	aScope
A disposable flexible intubation videoscope, the Ambu® aScope™, and the first experiences with awake intubation in	Yes	Poster presented, Manuscript in preparation. Please refer to protocol	aScope

patients with difficult airways 2010 Kristensen, MS., Fredensborg, B.,Hansen, CM., Tvede, MF., Society for Technology in Anesthesia annual meeting 2010		R-PS-7-2009/Kristensen Dr. Kristensen has consented to be contacted.	
Evaluation of the novel, single-use, flexible aScope for tracheal intubation in the simulated difficult airway and first clinical experiences 2010 Piepho T, Werner C, Noppens RR. Anaesthesia. 2010 Aug;65(8):820-5.	Yes, provided aScopes	Yes.	aScope
Use of the Ambu(®) aScope™ in 10 patients with predicted difficult intubation 2010 Pujol E, López AM, Valero R. Anaesthesia. 2010 Oct;65(10):1037-40.	Yes, provided aScopes	Yes.	aScope
The learning curve for using Ambu® aScope™ *Galindo-Menéndez S, López García A.Submitted to* SEDAR Magazine (Spanish Society of Anaesthesiology).2010	Yes, provided aScopes	Article not published. White paper written by Ambu Clinical Department is available. "*Evaluation of the Ambu aScope for nasal intubation on manikin".*	aScope

Use of Ambu aScope in a simulated difficult airway 2012 Enohumah K., Kuriakose D., Hu P. 2012 Will be presented at GAT scientific meeting 2012, Glasgow June 27-29th	No	Poster not presented yet. Will be presented at GAT scientific meeting 2012, Glasgow June 27-29th	aScope
Randomized controlled trial comparing the Ambu aScope with conventional fibreoptic bronchoscope in asleep orotracheal intubation of adult patients undergoing general anaesthesia 2012 Jun Keat Chan Ongoing trial	Yes, provided aScopes	Trial will be completed in August 2012.	aScope2
The role of the aScope in novices learning fibreoptic guided intubation 2012 Jun Keat Chan ***Probably commenced later 2012***	No		aScope2

Temporary title: Fatigue when holding Ambu aScope2 compared with a traditional fibrescope Ahmad I, Guys and St Thomas hospital, NHS Trust, London, UK ***Will be commenced later 2012***	No		aScope2
Flexible optical intubation via the Ambu Aura-I versus blind intubation via the single use intubating LMA – a randomized clinical trial ***2012 Hagberg, C.*** Ongoing trial	Yes	Recruitment ongoing	aScope2

Appendix 5

Ambu
Ideas that work for life

Declaration

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CVR. nr. 63644919

Ambu aScope System

We hereby declare that to Ambu's knowledge: Ambu aScope System has not caused nor contributed to any adverse events registered at MHRA, UK nor has Ambu aScope System been subject to any recalls as evaluated according to EU MEDDEV 2.12/1 rev.7 Medical devices vigilance system.

For and on behalf of Ambu A/S, Denmark

June 18, 2012

Kaja Tengbjerg, Regulatory Affairs Professional
Corporate Regulatory Affairs

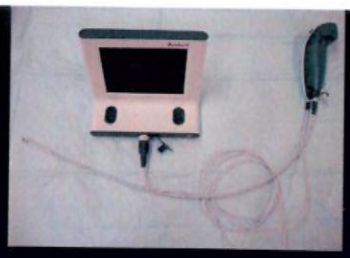
Appendix 6

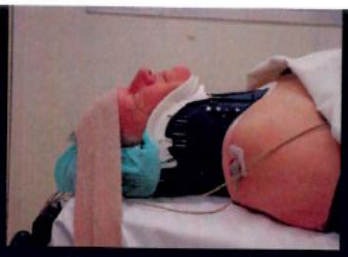
Suppress Items - Total is Null or Zero (Rows and columns)

Act Quantity	2009/10		2010/11			2011/12			All Time		
	aScope	Videoscope Intubation Disposable	aScope	aScope2	Videoscope Intubation Disposable	aScope	aScope2	Videoscope Intubation Disposable	aScope	aScope2	Videoscope Intubation Disposable
Asia	351	**351**	757	132	**889**	104	579	**683**	**1.212**	**711**	**1.923**
EMEA	3.944	**3.944**	3.439	1.977	**5.416**	531	4.645	**5.176**	**7.914**	**6.622**	**14.536**
US	338	**338**	966	270	**1.236**	22	1.865	**1.887**	**1.326**	**2.135**	**3.461**
All Sales Territories	**4.633**	**4.633**	**5.162**	**2.379**	**7.541**	**657**	**7.089**	**7.746**	**10.452**	**9.468**	**19.920**

jun 19, 2012 2:34:58 PM

Appendix 7





Comparison of the single-use Ambu aScope2® versus the fibreoptic bronchoscope for tracheal intubation in patients with cervical spine immobilization

P. Schoettker, V. Krugel, P. Frascarolo, I. Bathory

Anesthesiology Department, University Hospital Center and University of Lausanne, Switzerland

Introduction: Despite the emergence of new videoscopes, fibreoptic intubation remains a key technique for difficult airway management. Standard reusable bronchoscopes offer high quality vision but are expensive to purchase, in addition to maintenance. Recently, a single-use flexible videoscope has been developed with an updated device being commercialised (Ambu aScope2®) integrating a better quality optical system.

Aim: We planned a prospective randomized controlled clinical study to compare the Ambu aScope2® to a standard fibreoptic bronchoscope for tracheal intubation in 100 patients with a simulated difficult airway.

Methods: 100 patients (ASA 1 or 2 undergoing elective surgery with oro-tracheal intubation) were randomly assigned to group "aScope2®" or "fiberoptic bronchoscope". Exclusion criteria were BMI > 35, dental instability, previous difficult intubation or ear-nose-throat surgery. After standardized induction of general anesthesia and neuromuscular blockade, the neck was immobilized with an appropriately sized semi-rigid Philadelphia Patriot ® cervical collar and intubation performed by the same experienced anaesthetist. Demographics, time to indentify the carina, time to intubate (from touching the device to obtaining end-tidal CO2) and time to railroad the tube, intubation success, quality of vision as well as ease of intubation were recorded.

Results: Both groups were similar in terms of gender, ASA, weight, height and no statistically significant difference was noted in factors predictive of difficult intubation (MP, TMD and neck circumference). The median mouth opening was 2.0 cm [1.5;2.2].

All patients were successfully intubated in both groups within the set time limit (4 minutes).

The time was significantly shorter and the quality of vision significantly better in the standard fibreoptic bronchoscope group.

A jaw-thrust maneuver was significantly more often necessary in the aScope2® group (16 vs. 5 patients; p=0.01).

Four patients necessitated two attempts in the aScope2® group (secretions that lead to removal of the scope and lens cleaning), compared to eight with the fibrescope (p=0.22) due to secretions (1 patient), malpositionning of the Ovassapian split airway (2 patients) and accidental withdrawal of fibrescope during manipulation (5 patients).

	Quality of vision			Ease of intubation			Time [s]		
	Excellent	Acceptable	Unacceptable	Easy	Intermediate	Difficult	To see carina	To railroad tube	To intubate
Fibrescope	49*	1*	0	38	7	5	14.5 [11.8;22.0]*	31.5 [27.0;38.0]	49.5 [40.0;59.3]*
aScope2®	24*	22*	4	30	12	8	27.5 [22.0;45.8]*	34.0 [29.0;42.0]	69.5 [54.8;97.3]*

*: significant difference (p<0.05)

Conclusions: Evolution of technology has led to the design and commercialisation of a single-use flexible optic device. In simulated difficult airway patients, oro-tracheal intubation was always possible with this device, although with less quality of vision and longer time comparing to a standard fibreoptic bronchoscope. It might represent an alternative in cases of non-available expensive fibreoptic bronchoscopes or specific institutional situations.

We thank FLAVA (Fondation Latine des Voies Aériennes), www.flava.ch for financially supporting this study

Appendix 8

Re: Request of info on basis of the presentation on "Feasibility of a combined use of a video-laryngoscope with a novel flexible video-stylet for predicted difficult intubation"
Lenhardt,Rainer
to:
Sanne Wille
16-04-2012 14:33
Show Details

History: This message has been replied to.
Dear Sanne,

I am currently working on the manuscript. However, after some difficulties with the IRB I still need to include 5 more patients.
Thus, the study has not been completed, yet.
Basically, I have no new information regarding results as compared to the ASA abstract, that, I assume, you have handy.

I will present the final results at my talk for the Ambu research board in June

I do believe, that the data and manuscript have the potential to promote the use of the aScope. (I call it tracheoscope in the manuscript)

The use of the glidescope was random. The company lended me a glidescope. The study could have been done with any VLS

I hope you can be at the board meeting in Paris on June 8

Kind regards,
Rainer

Rainer Lenhardt, MD, MBA
Associate Professor
Vice-Chair for Clinical Affairs
Director, NeuroSciences/Anesthesia Critical Care Unit
Department of Anesthesiology
University of Louisville
Phone: (502) 852-3122
Fax: (502) 852-3762
Email: rainer.lenhardt@louisville.edu

On Apr 16, 2012, at 6:08 AM, Sanne Wille wrote:

> Dear Dr. Lenhardt,
>
> As a Clinical Research Specialist in Ambu, I am writing to you because I was interested to read your poster of feasibility of use of Glide Scope and aScope for predicted difficult intubation.

Ambu aScope has been selected to submission of a medical technology guidance by NICE(National Institute for Health and Clinical Excellence) in the NHS in UK. Some of the evidence which have been chosen to the submission is the presentation you have been involved in. In light of this, I have some questions which I hope you can help me with.

I would like to know the rationale behind the choice of Glidescope exactly, and not another VLS? And if data has been submitted to any publication?

I would also like to hear of the opportunity of getting access to the Clinical Investigation Report for the study.

Any information which can elaborate the study will be of great importance, since the framework and content is seen as important for the documentation of aScope's role in a difficult intubation procedure.

I really hope you will be able of assisting me with further information on the work that the poster is based on, which will be of highly importance for getting the aScope recognized as a suitable intubation device for difficult airways.

I look forward to hearing your feedback and please do not hesitate to contact me if you have any questions.

Best Regards

Sanne Wille
Clinical Research Specialist

Ambu A/S
Baltorpbakken 13
DK-2750 Ballerup Denmark

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Direct +4572252173
Mobile +4520807089
Fax +4572252055

Re: Request of info on basis of the presentation on "Feasibility of a combined use of a video-laryngoscope with a novel flexible video-stylet for predicted difficult intubation"
Lenhardt,Rainer
to:
Sanne Wille
17-04-2012 14:42
Show Details

History: This message has been replied to and forwarded.

Dear Sanne,

I have the protocol attached.
Please, treat it with confidentiality
The protocol has the number NCT01215695

Kind regards,

Rainer

On Apr 17, 2012, at 8:22 AM, Sanne Wille wrote:

> Dear Dr. Lenhardt,
>
> Thank you very much for your prompt and thorough answer.
> I know it is a bit much, but would it be possible to have access to the protocol which has formed the basis for the study?
> The reason for me asking is your study will be part of the primary evidence for the submission due to its CRT level being a randomized, prospective trial with 140 patients enrolled(or more), and therefore any information which can elaborate the abstract will be of great importance. Of course all information will be handled with confidentiality if requested so. The committee will take ongoing evidence into consideration as well, so even if the manuscript or data is not finalized it will still be valuable.
>
> I really hope you will be able to assist me with some information and I will have the opportunity to join the meeting in Paris and hear your presentation.
>
> Best Regards
>
> Sanne Wille
> Clinical Research Specialist
>
> Ambu A/S
> Baltorpbakken 13
> DK-2750 Ballerup Denmark
>
> Phone +4572252000
> Direct +4572252173
> Mobile +4520807089
> Fax +4572252055

<graycol.gif>"Lenhardt,Rainer" ---16-04-2012 14:33:41---Dear Sanne, I am currently working on the manuscript. However, after some difficulties with the IRB

From: "Lenhardt,Rainer" <rainer.lenhardt@louisville.edu>
To: Sanne Wille <SAWI@ambu.com>
Date: 16-04-2012 14:33
Subject: Re: Request of info on basis of the presentation on "Feasibility of a combined use of a video-laryngoscope with a novel flexible video-stylet for predicted difficult intubation"

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I look forward to hearing your feedback and please do not hesitate to contact me if you have any questions.

Best Regards

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Re: Request: data "feasibility of a combined use of a video-laryngoscope with novel flexible video-stylet for predicted difficult intubation"
Lenhardt,Rainer
to:
Sanne Wille
19-06-2012 19:22
Show Details

History: This message has been replied to.
Dear Sanne,

I understand your request.
I cannot release data, while I am in the middle of writing the manuscript.

Every publisher makes it quiet clear that the copyright is on them and data cannot be released before publication with the exception of abstracts.

I do hope that we will get the paper submitted soon.

NICE has to take the abstract and the protocol as the proof of feasibility for the moment.

I hope you understand my reasoning.

Kind regards,

Rainer Lenhardt

On Jun 19, 2012, at 5:10 AM, Sanne Wille wrote:

> Dear Dr. Lenhardt,
>
> As I have previously written, Ambu is in the middle of a process with the purpose of getting aScope approved by NICE in the United Kingdom.
>
> All clinical evidence has been submitted and I have now received a request from the panel from NICE, concerning the investigation you performed with aScope and Glidescope.
> Due to your trial being one of two primary studies, the panel would like to have access to the clinical investigation report.
> I have under confidentiality submitted the protocol together with your poster presentation, but they would like to have access to the full data to be able to relate to aScope's performance in the given situation.
>
> I do realize it's a lot to ask for, but I can only stress it is of great importance in assessing the performance of aScope and thus improve the clinical treatment of the patient.
>
> I hope you will understand and help me with this query and I do want to emphasize that all data will be handled in strictest confidence and not be an obstacle to your work with publishing.
>
> Best Regards
>
> Sanne Wille
> Clinical Research Specialist

Appendix 9

Re: Request of information on the presentation"Evaluation of the Ambu aScope2 in eight patients with anticipated difficult airways having awake fibre-optic intubations".
Ahmad Imran (GUY'S AND ST THOMAS' NHS FOUNDATION TRUST)
16-04-2012 14:01
To:
Sanne Wille
Show Details

History: This message has been replied to.
Dear Sanne,

Thank you for your email and interest in our studys

1] We did submit a series of 12 cases to Anaesthesia, but they said it wasnt something they were likely to publish, so we will be re-submitting it to one of the european journals, such as EJA etc... I will keep you updated on the progress

2] By Clinical Investigation report, if you mean ethics approval, we did ask our local ethics team and they said we didnt need to apply for it as these patients would all require awake FOI anyway, so we did not formally apply for ethical approval

3] the poster is based on work we did at our institution (a tertiary referral centre ofor head and neck cancer and airway surgery) last year. 3 airway experts used the Ambu aScope 2 on 12 patients with predicted difficult airways. They all underwent awake FOI and various parameters were recorded, such as time to intubation, view obtained, manoeuvrability of scope, ease of railroading ETT etc.

4] we have collected data on about 35 anaesthetists comparing onset of fatigue when holding the ambu aScope2 as compared with a traditional fibrescope. The results are being analysed so we should have them back soon

I hope that helps,

best wishes,

Dr Imran Ahmad FRCA
Consultant Anaesthetist
Guy's & St Thomas' NHS Foundation Trust
London, UK

On 16 Apr 2012, at 12:43, Sanne Wille wrote:

> Dear Dr. Ahmad,

> Dear Dr. Ahmad,
>
> As a Clinical Research Specialist in Ambu and a colleague of David Edwards, I am writing to you because I with interest have read your poster regarding an

evaluation of the Ambu aScope 2 in anticipated difficult airways.

As part of an aScope submission, the presentation you have been involved in has been selected as documentation for the aScope performance. In light of this, I have some questions which I hope you can help me with, please.

I would like to know the if the data has been submitted to any publication?

I would also like to hear of the opportunity of getting access to the Clinical Investigation Report for the study. Any information which can elaborate the study will be of great importance, since the framework and content is seen as important for the documentation of aScope's role in a difficult intubation procedure.

I really hope you will be able of assisting me with further information on the work that the poster is based on, which will be of highly importance for getting the aScope recognized as a suitable intubation device for difficult airways.

I am also working on an overview of available and ongoing clinical documentation on aScope, and as regards to that David Edwards informed of an ongoing study which involves aScope and fatigue of the clinician during use. Is that something you will be able to reveal a bit more of?

I look forward to hearing your feedback and please do not hesitate to contact me if you have any questions.

Best Regards

Sanne Wille
Clinical Research Specialist

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Request: Further information on "Evaluation of the Ambu aScope2 in eight patients with anticipated difficult airways having awake fibre-optic int

Sanne Wille to: Ahmad Imran (GUY'S AND ST THOMAS' NHS FOUNDATION TRUST) 20-06-2012 13:01

Dear Dr. Ahmad,

As I have previously written, Ambu is in the middle of a process with the purpose of getting aScope approved by NICE in the United Kingdom.

All clinical evidence has been submitted and I have now received a request from the panel from NICE, concerning the investigation you performed with Ambu aScope 2.
Due to your evaluation being important for documenting the performance of aScope, the panel would like to have access to the clinical investigation report to be able to relate to aScope's performance in the given situation. By clinical investigation report I mean the file where you have recorded the observations in relation to the endpoints. The purpose of getting access to the full data is for NICE to be able to relate to aScope's performance in its right clinical settings.

I do realize it's a lot to ask for, but I can only stress it is of great importance in assessing the performance of aScope and thus improve the clinical treatment of the patient.

I hope you will understand and help me with this query and I do want to emphasize that all data will be handled in strictest confidence and not be an obstacle to your work with publishing.

Best Regards

Sanne Wille
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[redacted]

MEMO

Ambu
ideas that work for life

Jakob B. Kristensen (JBK)
24-02-2011

TNQ
24.02.2011

To: JBK, TFR

From: TNQ Date: 24.02.2011

cc:

Re.: Doc. no.: 314000-0615a301 Product Validation NXT

Product Validation activities performed on aScope NXT

1 Introduction

For insuring that the sterile single patient use Ambu aScope and the reusable Ambu aScope monitor were ready for sale, the system have undergone a product validation. Refer to [1]. The validation of the Ambu aScope system was performed under simulated conditions imitating a real user condition.
Based on the changes made to the single use aScope product in relation to the aScope NXT project, additional product validation activities have been needed.

2 Content of product validation performed on aScope

The product validation took place in Denmark. The Ambu aScope system was prepared and used as described in the Instruction for Use. The users had beforehand received the IFU, the aScope Mini IFU and the quick guide and they had prepared themselves by reading the content. The product validation was performed covering all important aspects in relation to the use such as:

- Reading and understanding the IFU, the Mini IFU and the quick guide
- Opening of the pouch containing the aScope product
- Connecting the aScope product to the aScope monitor
- Turning on the aScope monitor
- Turning on the aScope single use product
- Evaluation of the picture quality of the monitor
- General usage of the aScope product when doing intubation procedures

The conclusion to the performed product validation was a rating of the system between acceptable and good. For a more detailed description refer to [1].

In general the performed product validation was extensive covering all important aspects in relation to the aScope product, the usage of the aScope product, the aScope monitor and its use and the usage of the complete system and its interface.

3 Additional product validation activities needed on aScope NXT

In relation to the aScope NXT project neither the functionality of the aScope product nor the functionality of the aScope monitor has been changed. However, due to feed-back received from user the following have been updated on the single use aScope product, hereafter called aScope NXT:

- New lens design for improving the cleanability during use
- A flow connector has been added for a possible oxygen connection to the working channel on the aScope NXT.
- A protective foam has been added to the packaging for adding extra safety during handling.

3.1 Product Validation of new lens design

The new lens design consists of an additional lens cover making the outer surface of the lens flat and without the concave shape of the old lens design. A lens being flat should make the cleaning of the lens during use more easy. The cleaning has been tested at a pig test performed at Panum, Copenhagen in January 2011. This testing involved 3 doctors in total using 18 aScope NXT products. During the testing the aScope NXT product was compared to a competitor product from Olympus. The updated lens design performed very convincing during this testing. Refer to [2].

3.2 Product Validation of flow connector

A flow connector has been added to the aScope NXT. The flow connector has a luer connection making it possible to connect the flow connector to the existing luer connector on the aScope NXT. The flow connector gives the user a possibility of supplying oxygen or air through the working channel of the aScope NXT. The handling such as connecting the flow connector and supplying oxygen has been evaluated by 4 doctors. None of the 4 doctors experienced any problems in handling the flow connector. Refer to pig test performed at Panum, Copenhagen in September 2010 [3].

3.3 Product Validation of protective foam

A protective foam has been added to the tip of the camera. The foam has been added as extra safety in case of very rough handling of the boxes. The foam has not been added due to known problems but only for adding extra safety to the camera unit. The instructions of removal of the foam are described in the IFU and furthermore is the flow connector in a red material making it visible to the user. In the light of this no further actions have been taken in relation to product validation.

4 Conclusions

When launching the single use aScope product and the reusable aScope monitor a complete and thorough product validation was performed with a positive result.

In relation to the aScope NXt project a few updates have been done to the single use aScope product. The reusable aScope monitor is unchanged. As the updates done to the aScope are minor a complete new product validation is not performed. Instead each one of the updates have either been successfully validated or an evaluation has been made for not performing any further actions.

Therefore no further product validation is needed prior to launch of the aScope NXT product.

5 References

[1] 314000-0615a201 aScope product validation
[2] 314000-0803t101 Pig test, Panum January 2011
[3] 314000-0803s301 Pig test, Panum September 2010