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1 Title of the project

Sedation in intensive care

2 Name of TAR team and project lead

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3 Plain English summary

Sedation involves administration of one or more drugs to produce a state of calm or sleep in the patients. Sedation is important in the intensive care unit (ICU) as patients often require invasive or uncomfortable procedures. The goal of sedation in this context is to minimise pain and discomfort, protect from stressful or harmful events, inhibit anxiety, and promote sleep and amnesia.

Sedation practice in the ICU has changed over the years. The tradition of deep levels of sedation has moved towards lighter sedation as there is evidence for improvements in both short term and longer term clinical and psychological outcomes. Two assessment tools are commonly used for monitoring the patients' level of sedation in ICUs: the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale. In addition, interruption of sedation on a daily basis has been proposed for assessing the level of sedation and avoiding under- or over-sedation.

A variety of drugs may be used for sedation. The most frequently used are propofol, benzodiazepines, (e.g. midazolam, lorazepam, diazepam) and α_2-agonists (i.e. clonidine; dexmedetomidine). Each of these drugs varies in the length of time until onset of effects, duration of effects, and side effects. None has been shown to be superior to all others. However, α_2-agonists produce a different pattern of sedation as compared to other sedative drugs, with sedated patients being more able to communicate their needs without experiencing the breathing difficulties associated with other drugs.

The aim of the present assessment is to bring together the existing evidence on the effects of dexmedetomidine versus clonidine and of dexmedetomidine or clonidine versus alternative sedative drugs including propofol and benzodiazepines for sedation of mechanically ventilated adults admitted to ICUs.

4 Decision problem

4.1 Background

Sedation is "the administration of pharmacological agents designed primarily to induce a sedative effect in patients".[1] Sedation is a key component of the care of critically ill patients, who often require potentially invasive or uncomfortable procedures, such as mechanical ventilation.[1-3] Indications for the use of sedation in intensive care unit (ICU) include: to alleviate pain; to facilitate the use of distressing procedures and minimise patient discomfort; to provide protection from stressful and harmful stimuli; to reduce anxiety and control agitation; to enable nocturnal sleep and, where necessary, amnesia (unpublished study, S Harvey, ICNARC, 2014).[3,4] Sedation requirements vary widely between patients and sedative regimens ought to be tailored to the individual patient needs (unpublished study, S Harvey, ICNARC, 2014).

Evidence from randomised controlled trials (RCTs) and current guidelines supports the use of the minimum possible level of sedation to achieve the desired clinical effects without compromising patient comfort and safety (unpublished study, S Harvey, ICNARC, 2014).[5,6] A review of international surveys of critical care clinicians published between 1999 and 2009 has confirmed that the current trend is towards lighter levels of sedation.[7] There may, however, be specific situations that require deep sedation or general anaesthesia (unpublished study, S Harvey, ICNARC, 2014).

The optimal sedation level varies according to the patients' clinical conditions and their treatment requirements. Generally, sedation level is measured by ICU staff by means of scoring sedation scales. Several scales have been developed to monitor sedation levels in critically ill patients. The first standardised measurement for sedation was the Ramsay Sedation Scale (RSS)[8] which has been recently superseded by the Richmond Agitation-Sedation Scale (RASS)[9,10] and the Riker Sedation-Agitation Scale (SAS).[11] Scores on the RASS range from +4 (combative) to -5 (cannot be aroused). Riker SAS scores range from 7 (dangerous agitation) to 1 (cannot be aroused). For mechanically ventilated critically ill patients, target scores of between -2 and 0 for the RASS or 3 to 4 for the SAS are considered appropriate. Other objective measures of sedation include the Bispectral Index, which measures the level of consciousness by an algorithmic analysis of the patient's electroencephalogram, and haemodynamic parameters such as the heart rate and the arterial pressure .[12-14]

Sedation requirements are often not optimally managed and poor sedation practice, which encompasses under-sedation and over-sedation, may have important detrimental effects.[1,15] Under-sedation can cause agitation, inadequate ventilation, hypertension, tachycardia and discomfort[16] while over-sedation may be responsible for prolonged mechanical ventilation and weaning, hypotension and under-perfusion, thrombosis and DVT, and an increase in delirium (unpublished study, S Harvey, ICNARC, 2014).[17] A variety of strategies have been proposed to improve management of critically ill patients in ICUs including use of sedation guidelines, protocols, and goal-directed sedation algorithms[17-20] light target level of sedation and daily sedation interruptions [21-25] and regular monitoring of sedation requirements.[26] The recent Clinical Practice Guidelines from the Society of Critical Care Medicine for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (PAD guidelines) strongly recommend the use of management guidelines and protocol in ICUs[5]. In a recent UK national survey just over 57% (122/214) of the assessed ICUs reported the use of a written sedation protocol (unpublished study, S Harvey, ICNARC, 2014). The PAD Guidelines recommend also daily sedation interruption or a light level of sedation in mechanically ventilated adult ICU patients.[5] Current evidence on the use of daily sedation interruptions (DSIs) is far from being conclusive. A RCT by Girard and colleagues conducted in four tertiary-care hospitals has shown that a strategy consisting of both daily spontaneous breathing attempts and daily spontaneous awakening attempts, resulted in better outcomes than standard

approach.[27] A meta-analysis of five trials published in 2011 highlighted the need for further RCTs with long-term survival follow-up before daily sedation interruption could become standard sedation practice for critically ill patients.[28] A multicenter RCT by Mehta and colleagues[7] found that among mechanically ventilated patients receiving continuous sedation, the combined use of protocol-guided sedation and DSI did not improve the clinical outcomes observed with protocol-guided sedation alone. Similarly, a recent Cochrane systematic review has not provided strong evidence that DSIs influence the duration of mechanical ventilation, mortality, length of stay, drug consumption, quality of life, or adverse events compared to sedation strategies that do not include DSIs. It is worth noting, however, that the authors considered the results unstable due to the small number of identified trials, the clinical and statistical heterogeneity observed among them, and the fact that the overall estimate of effect was only marginally significant. Moreover, a reduction in the duration of mechanical ventilation was detected when the analyses were restricted to trials conducted in North America.[29]

Prior to initiating sedation, it is important to provide appropriate analgesia to all critically ill patients.[1,13,30] Often patients in ICUs experience pain at rest and as a consequence of routine critical care. Pain is reported as the principal stressor by patients and is the most common memory they have of their ICU stay.[6,31] The PAD Guidelines stress the importance of routine assessment of pain and provision of pre-emptive analgesia.[5] Adequate pain control can also reduce the need for sedative drugs.[32] Albeit sedatives and analgesics work in synergy, they have discrete targets.[3] Some analgesics may have a secondary sedative effect.[1] Remifentanil, an opioid, for example, can be used as a sole agent due to its sedative effects.[6] The patient requirements for analgesia and sedation should be thoughtfully considered and sedation should never be given as a substitute for analgesia (unpublished study, S Harvey, ICNARC, 2014).

Alongside assessment of pain, the PAD Guidelines recommend the routine monitoring of delirium.[5] Delirium occurs in 60% to 80% of mechanically ventilated patients in ICUs.[33] Delirium is associated with higher mortality, prolonged duration of mechanical ventilation, longer hospital stay, and an increased risk of cognitive impairment among adult ICU patients.[24,34,35] The tools most commonly used to assess delirium and recommended by current guidelines[5] are the Confusion Assessment Method for the ICU (CAM-ICU)[36] and the Intensive Care Delirium Screening Checklist (ICDSC).[37]

A variety of medications may be used to treat critically ill patients in ICUs. The choice of sedative or analgesic agents to achieve an optimal level of sedation can be quite challenging and needs to take into consideration the pharmacological properties of the different drugs as well as the individual patients characteristics and needs.[7,13] Sedative agents commonly used in ICUs include propofol, benzodiazepines (midazolam, diazepam, lorazepam), and α_2-agonists (clonidine, dexmedetomidine).[24] Analgesic agents include morphine, fentanyl, alfentanil, remifentanil.[7,30] The general trend, both in the

UK and internationally, is currently moving from benzodiazepines to propofol and from morphine to alfentanil, fentanyl and remifentanil (unpublished study, S Harvey, ICNARC, 2014).[7,38,39] The 2013 PAD Guidelines suggest that sedation strategies using non- benzodiazepines (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam).[5] The 2014 Intensive Care National Audit & Research Centre (ICNARC) national survey conducted among 235 adult general ICUs in the UK has shown that propofol is the most widely used sedative agent (88% of the units reported that was the first choice of agent). Approximately a third of the surveyed units (32%) reported frequent use of midazolam but only in 6% of them was reported to be the first choice of sedative agent. Around a third of the surveyed ICUs (33%) reported frequent use of clonidine while 10% of them reported frequent use of dexmedetomidine. The most frequently used agents for analgesia were alfentanil (51% of the units), morphine (42%), and fentanyl (36%) with a trend away from morphine, which was the first choice of analgesic agent in only 20% of the units, toward alfentanil and fentanyl (unpublished study, S Harvey, ICNARC, 2014).

Intravenous anaesthetic agents

Propofol is a short-acting intravenous general anaesthetic agent commonly used in ICUs since the 1980s. It activates gamma -amino butyric acid (GABA A) receptors and has shown a considerable array of effects including anxiolysis, anticonvulsant activity, anti-emesis, and ability to reduce intracranial pressure (unpublished study, S Harvey, ICNARC, 2014). [6,40-44] Propofol is a lipid soluble compound with a rapid onset of action (from seconds to minutes) and a short duration of effect following short-term administration.[5,41,45] Because of its short duration of sedative effect, propofol may be indicated for patients who require frequent awakening and DSIs.[5,46] The half-life of propofol ranges from 30 to 60 minutes after short-term infusion but longer after prolonged infusion (up to 50±18.6 hours).[5,6] The rapid onset and offset are specific features of propofol compared with other common sedative drugs.[47] The most significant side effects of propofol include hypotension due to systemic vasodilation and dose-dependent respiratory depression. Other side effects include hypertriglyceridemia, acute pancreatitis, arrhythmia, bradycardia and cardiac arrest.[5,6,13] Propofol administration may rarely cause propofol infusion syndrome: an adverse reaction characterised by lactic acidosis, hypertriglyceridemia, hypotension and arrhythmia.[5]

A systematic review of 16 RCTs with a total of 1,386 critically ill adult patients, which compared propofol with alternative sedative agents for medium or long-term sedation, concluded that propofol was safe and could reduce the duration of mechanical ventilation. Propofol reduced also the length of ICU stay when compared to long active benzodiazepines but not when compared to midazolam.[48]

Benzodiazepines

Benzodiazepines bind the GABA receptor complex modulating GABA release in the central nervous system causing down-regulation of neuronal excitation (neurons become less excitable).[13] According to the doses used they can cause sedation, anxiolysis or hypnosis (unpublished study, S Harvey, ICNARC, 2014). Benzodiazepines vary in their potency, onset and duration of effect, uptake, distribution, metabolism and presence or absence of active metabolites.[30,45] Lorazepam is more potent than midazolam, which in turn is more potent than diazepam. As midazolam and diazepam are more lipid soluble than lorazepam, they cross the blood brain barrier quicker and result in a more rapid onset of action (2 to 5/10 minutes) than lorazepam (5 to 20 minutes).[6,13,49-51]The half-life of midazolam is 3 to 11 hours, compared with 8 to 15 hours for lorazepam and with 20 to 120 hours for diazepam.[5,6] Midazolam and diapezam metabolites are active and they tend to accumulate with prolonged administration, especially in patients with renal dysfunction.[13,52] Lorazepam metabolites are not active and for this reason it is the preferred benzodiazepine in patients with renal failure.[13] As all benzodiazepines are metabolised predominantly in the liver, clearance is reduced in patients with hepatic dysfunction.[5] Adverse effects of benzodiazepines include hypotension, respiratory depression, paradoxical agitation, tolerance with acute discontinuation and delirium.[6,30,53]

A recent systematic reviews of six trials (1,235 patients) concluded that the use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepines-based regimen in critically ill patients may reduce ICU length of stay and duration of mechanical ventilation.[54] Indeed, current PAD guidelines suggest that sedation strategies using non-benzodiazepines (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve outcomes in mechanically ventilated adult ICU patients.[5]

Alpha-2 agonists

Dexmedetomidine is a newer selective α_2- receptor agonist, which has sedative, analgesic, anxiolytic and sympatholytic effects (unpublished study, S Harvey, ICNARC, 2014).[5,13,55] The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem.(SPC) The α_2- agonists pattern of sedation is quite different from that of other sedative agents in that patients can be aroused readily and their performance on psychometric tests is usually well preserved (Intensive Care Society Review 2014).[56,57] Moreover, dexmedetomidine does not depress the respiratory system, unlike other sedative agents.[58,59]

In clinical trials dexmedetomidine has shown to be similar to midazolam and propofol on the time in target sedation range in a predominantly medical population requiring prolonged light to moderate sedation (RASS 0 to -3) in the ICU for up to 14 days,[60,61] reduced the duration of mechanical ventilation compared to midazolam[60,62,63] and reduced the time to extubation compared to midazolam

and propofol. Compared to both propofol and midazolam, patients receiving dexmedetomidine were more easily roused, more cooperative and better able to communicate whether or not they had pain[60,62] and showed a lower rate of post-operative delirium.[58,63,64] The sedative benefits of dexmedetomidine compared with midazolam are, however, not conclusive. A systematic review of six RCTs (1,031 intensive care patients) published in 2013 has highlighted the need for further, more robust, research since, so far, the evidence of the advantages of dexmedetomidine versus midazolam in the ICU setting is limited.[2] Another meta-analysis of 27 RCTs assessing dexmedetomidine versus any other comparator in 3,648 mechanically ventilated ICU patients indicated that dexmedetomidine could be useful in reducing ICU stay and time to extubation even though heterogeneity was detected among included studies.[65] recent meta-analysis of 14 trials (3,029 critically ill patients) has showed that compared with other sedative agents the use of dexmedetomidine in ICUs is associated with a significant reduction in the incidence of delirium, agitation and confusion.[66]

The dexmedetomidine terminal elimination half-life is around 2 hours.[5,6] Main adverse effects related to dexmedetomidine are hypotension and bradycardia.[6,13,67] Transient hypertension may occur during loading infusion.[6]. The European Commission granted a marketing authorisation valid throughout the European Union for dexmedetomidine (Dexdor) in September 2011.[68]

Clonidine acts centrally by stimulating α_2-adrenergic receptors and producing a reduction in sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate.[69] Originally marketed as an antihypertensive agent, clonidine has demonstrated sedative and analgesic-sparing properties. The current therapeutic indications include the prophylactic management of migraine or recurrent vascular headache and the management of vasomotor conditions commonly associated with the menopause. In the ICUs, it has been introduced as an alternative for the treatment of delirium or as a second-line sedative agent.[70-72] The pharmacodynamics pattern of clonidine is broadly similar to that of dexmedetomidine, but dexmedetomidine is more specific for α_2- receptors and has higher affinity for the alpha2-adrenoceptors than clonidine.[55] Clonidine alone has shown to be effective in controlling delirium and withdrawal syndromes from opioids, benzodiazepines, nicotine and alcohol (Intensive Care Society Review 2014).[70,73-76] Clonidine is a very lipid soluble agent. The peak action occurs 10 minutes and lasts for 3 to 7 hours after a single intravenous dose. The elimination half-life is 6-23 hours (average 7.7 hours) (unpublished study, S Harvey, ICNARC, 2014).[77,78] Sudden cessation of clonidine after prolonged use may cause a withdrawal syndrome leading to rebound hypertension and tachycardia in susceptible patients.[30,72,79] Clonidine is metabolised in the liver and is eliminated primarily through the kidney. Main adverse effects include hypotension, bradychardia and xerostomia.[80]

The role of clonidine and dexmedetomidine in the sedation of ICU patients has yet to be fully established.

4.2 Purpose of the decision to be made

An evidence synthesis of the effects of α_2-agonists versus alternative sedative agents used in clinical practice with the purpose to inform any future RCT.

The specific objectives of this assessment are:
i) To assess the effects of sedation with dexmedetomidine compared with clonidine in mechanically ventilated adults admitted to ICUs;
ii) To assess the effects of sedation with dexmedetomidine or clonidine compared with other most commonly used sedative agents (i.e. propofol and benzodiazepines), in mechanically ventilated adults admitted to ICUs.

4.3 Clear definition of the intervention

Dexmedetomidine is an alpha2-agonist agent with a UK marketing authorisation *"For sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to RASS 0 to -3)."*[68] According to the summary of product characteristics, dexmedetomidine is for hospital use only and should be administrated by a healthcare professional skilled in managing patients requiring intensive care. It should only be administered by intravenous infusion using a controlled infusion device. Doses are adjusted until the required level of sedation is attained. A loading dose is not recommended as it is associated with increased adverse reactions. The maximum dose of dexmedetomidine is 1.4 micrograms/kg/h. During infusion, all patients should have continuous cardiac monitoring and respiration should be monitored in non-intubated patients. Use of dexmedetomidine for longer than 14 days requires monitoring and regular assessments. The combined use of dexmedetomidine with anaesthetics, other sedatives, hypnotics or opioids is likely to enhance pharmacological effects and consequently a reduced dosage of dexmedetomidine or the concomitant drug may be necessary.

Clonidine is available as 25 micrograms tablets or as ampoules of 150 micrograms in 1ml solution for injection. At present clonidine does not have a marketing authorisation as a sedative agent and the summary of product characteristics do not provide dosage recommendations for sedation. The UK Intensive Care Society Review of Best Practice for Analgesia and Sedation in the Critical Care states that the usual dose by infusion is 0.5-2.0 micrograms/kg/hr (unpublished study, S Harvey, ICNARC, 2014).

4.4 Place of the intervention in the treatment pathway(s)

Sedatives should be prescribed according to validated sedation scales and protocols and a variety of strategies have been proposed. Every sedation strategy needs to balance short-term benefits, such as decrease in period of mechanical ventilation, and long-term effects.[13,68] Utilising a protocol for sedation could improve sedation by integrating regular assessments of patients and proposed changes to sedatives and/or analgesics.[1]

Current USA guidelines issued by the American College of Critical Care Medicine in conjunction with the Society of Critical Care Medicine and American Society of Health-System Pharmacists[5] and German guidelines issued by the Working Group on Analgesia, Sedation and Delirium Management in Intensive Care[81] recommend assessment and treatment of pain, followed by sedation as well as by the assessment and treatment of delirium. A recent survey prepared by the UK Intensive Care Society (unpublished study, S Harvey, ICNARC, 2014) describes a generic sedation framework for providing analgesia and sedation to ICU (Figure 1), which is in line with the USA and German models of care.

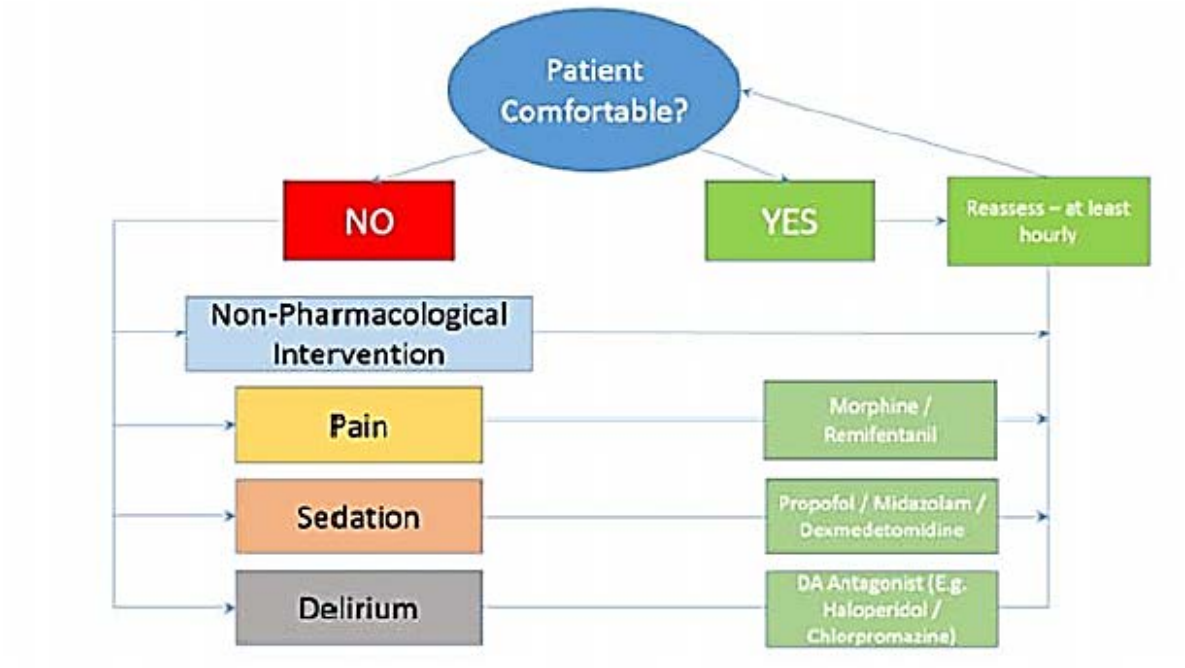

Figure 1 A general framework for analgo-sedation in ICU (the list of drugs is not exhaustive)
Source: 2014 UK Intensive Care Society Review of Best Practice for Analgesia and sedation in the Critical Care.

4.5 Relevant comparator(s)

Comparators for this assessment will be the most commonly used sedative agents according to the 2014 ICNARC national survey: propofol and benzodiazepines such as midazolam, lorazepam, and diazepam (unpublished study, S Harvey, ICNARC, 2014).

Propofol is a general anaesthetic agent and is available as a 1% or 2% emulsion for injection or infusion. For ICU use, continuous infusion is recommended, with the infusion rate being determined by the desired level of sedation. For mechanically ventilated patients propofol should be administrated slowly with a continuous infusion in order to titrate to the desired level of sedation and reduce the risk of hypotension. Most patients require maintenance rates of 0.3mg to 3mg/kg/h or higher (unpublished study, S Harvey, ICNARC, 2014).

Midazolam is a short-acting, water-soluble benzodiazepine, which is available as 2mg/ml or 5 mg/ml solution for injection. For ICU sedation, the recommended intravenous loading dose - 0.03 to 0.3mg/kg -should be given slowly in increments. Each increment of 1 to 2.5mg should be injected over 20 to 30 seconds, allowing 2 minutes between successive increments. Maintenance doses range from 0.03 to 0.2 mg/kg/h.[51]

Lorazepam is a benzodiazepine which is available in tablet form (1mg and 2.5mg) and as a solution for injection. Dosage and duration of treatment with lorazepam should be individualised, with the lowest effective dose being prescribed for the shortest possible time. Treatment should always include a withdrawal period and clinical evaluation is recommended prior to extension of use. Dosage of lorazepam for sedation use is not stated in the summary of product characteristics.

Diazepam is a benzodiazepine which is available as tablets or solution for injection. Recommended dosage of diazepam tablets as an anxiolytic is 5mg to 30mg daily, in divided doses. The lowest effective dose and shortest possible duration of treatment should be used. Dosage regimes should be evaluated every four weeks and treatment should not last longer than 8 to 12 weeks, including the withdrawal process. Intravenous injections of diazepam should be administered slowly (1.0ml solution/minute) to reduce the potential of adverse effects. The recommended dosage as an anxiolytic is 10mg. Where intravenous diazepam is to be administered concurrently with a narcotic analgesic agent (e.g. fentanyl), it is recommended that diazepam be given after the analgesic and that the dose be carefully titrated. Dosage of diazepam for sedation use is not stated in the summary of product characteristics.

4.6 Population and relevant sub-group(s)

The population under consideration is adults in ICUs who are mechanically ventilated. Patients with primary brain injuries (e.g. trauma or intra-cerebral bleed/infarct) will not be considered suitable for inclusion as the nature of their clinical conditions require a very specific ICU management and usually a deeper level of sedation/analgesia.

If data allow, sub-groups analyses will be performed according to age, severity of disease, different duration of mechanically ventilation; admission to ICU after elective surgery; nurse/patient ratio.

4.7 Key factors to be addressed

5 Report methods for synthesis of evidence of clinical effectiveness

An objective synthesis of the evidence for the relative clinical effectiveness of dexmedetomidine versus clonidine and of dexmedetomidine or clonidine versus other sedative agents including propofol and benzodiazepines such as midazolam, lorazepam, diazepam will be conducted according to the general principles of the NICE methods of technology appraisal.[82] In particular, evidence on relevant outcomes will be obtained from a systematic review of the relevant literature. The systematic review will be conducted according to the general principles of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[83] the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,[84] and the PRISMA statement for the reporting of systematic reviews and meta-analyses.[85]

5.1 Population

The population considered will be critically ill adults in intensive care units who require mechanical ventilation (see also section 4.6 above).

5.2 Intervention(s)

The intervention under consideration will be dexmedetomidine and clonidine.

5.3 Comparator(s)

The comparators considered will be propofol and benzodiazepines such as midazolam, lorazepam, diazepam.

5.4 Outcomes

The following outcomes will be considered:

Primary outcomes

i. Mortality

ii. Duration of mechanical ventilation
iii. Ventilator free days
iv. Length of ICU stay
v. Adverse events as reported by trials investigators and including:
    - rate of hypotension;
    - rate of hypertension,
    - rate of bradycardia,
    - rate of respiratory depression,
    - rate of delirium,
    - rate of coma,
    - rate of non-planned/accidental removal of lines (e.g. extubation) or catheters
vi. Unpleasant side effects as reported by trials investigators (e.g. unpleasant memories, constipation, diarrhoea).

Secondary outcomes

vii. Duration of weaning (time from weaning to extubation)
viii. Time spent in target sedation range
ix. Proportion of patients in target sedation range
x. Discharge readiness
xi. Extubation readiness
xii. Length of hospital stay
xiii. Quality of life
xiv. Costs

5.5 Search strategy

Comprehensive literature searches, using an appropriate combination of controlled vocabulary and text terms, will be conducted to identify reports of published, ongoing and unpublished studies reporting the clinical effectiveness of dexmedetomidine or clonidine in comparison with propofol and midazolam in mechanically ventilated adults admitted to ICUs. Highly sensitive search strategies will be designed, including appropriate subject headings and text word terms, interventions under consideration and relevant study designs. Searches will be run from 1999. A draft MEDLINE search is reported in Appendix 1. Databases to be searched include MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index, Biosis and the Cochrane Controlled Trials Register. Reports of relevant evidence synthesis will also be sought from the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects. Searches for

ongoing studies will be undertaken of the WHO International Clinical Trials Registry, Current Controlled Trials and Clinical Trials.gov.

Recent conference proceedings of key organisations will also be searched for relevant reports and will include the Critical Care Congress (SCCM), European Society of Intensive Care Medicine Annual Congress, International Symposium on Intensive Care and Emergency Medicine and Association of Anaesthetists of Great Britain and Ireland Annual Congress. Websites of regulatory bodies and HTA agencies will be checked for relevant unpublished reports while websites of relevant pharmaceutical companies and professional organisations will be searched for further pertinent information and reports. In addition, reference lists of all included studies will be perused for further citations.

5.6 Inclusion criteria

Evidence from RCTs comparing dexmedetomidine with clonidine or dexmedetomidine or clonidine with any of the comparator interventions will be suitable for inclusion. Trials may include one or more comparator interventions. A preliminary scoping search indicates that it is likely that no, or very limited, evidence is available from head-to-head RCTs comparing dexmedetomidine with clonidine.

5.7 Exclusion criteria

The following types of report will not be considered suitable for inclusion:

i. Narrative reviews, editorials and opinions
ii. Case reports
iii. Conference abstracts for which a full publication or further methodological information could not be found
iv. Non-English language reports for which a translation cannot be organised.

Studies that focus predominately on patients with primary brain injuries will be excluded.

5.8 Data extraction strategy

Two reviewers will independently screen all titles and abstracts identified by the search strategies. Full text versions of all potentially relevant reports will be retrieved and assessed independently by the same two reviewers. Any disagreements will be resolved by discussion or arbitration by a third reviewer.

A data extraction form will be developed and piloted for the purpose of this assessment. For each included study, information on geographical location, sponsor, study design, characteristics of participants, setting and characteristics of ICU practice (e.g. use of sedation assessment tools and protocols; nurse to patient ratio), characteristics of interventions and outcome measures will be

recorded if reported. One reviewer will complete the data extraction form for all included studies and a second reviewer will check the data extracted. Any disagreements will be resolved by discussion or arbitration by a third reviewer.

5.9 Quality assessment strategy

Two independent reviewers will assess the methodological quality of selected RCTs. Any disagreements will be resolved by consensus or arbitration by a third reviewer. Studies will not be included or excluded on the basis of their methodological quality.

The quality of all the included RCTs will be evaluated using the Cochrane Risk of Bias tool.[84] The following quality domains will be assessed: sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting.

Any relevant systematic reviews will be assessed using AMSTAR (assessing methodological quality of systematic reviews) tool.[86]

5.10 Methods of data synthesis

Where the same outcome is assessed by more than one included study, a quantitative synthesis of results will be conducted. Results of each study will be tabulated and summarised according to type of study design for each outcome and plotted as point estimates with corresponding 95% confidence intervals. Mean differences will be reported for continuous outcomes and risk ratios for dichotomous outcomes. Heterogeneity between studies will be assessed by visual inspection of forest plots and using the Chi^2 and I^2 statistics. If there is no evidence of heterogeneity, then pooled summary estimates will be derived from fixed-effects meta-analyses. Where significant heterogeneity exists, random effects meta-analyses will be used with the inverse-variance method and potential sources of heterogeneity will be assessed. Narrative syntheses will be conducted under any circumstances where a quantitative synthesis is not feasible or appropriate.

Where data permit, stratification according to age and disease severity score will be attempted.

If networks of evidence from RCTs exist, a Bayesian random effect networks meta-analysis implemented in WinBUGS[87] and based on MCMC methods to assess the relative effectiveness of the competing interventions will be performed. This will be done using the generalised linear modelling framework outlined by Dias and colleagues[88] and the appropriate link function for each outcome included in these analyses. This method allows the combination of direct and indirect treatment

effects for all pairs of treatments within the network. Treatment effects will be summarised by the median and 95% credible interval of the posterior distribution. We will also derive probabilities for each treatment in the network being the most effect. Additional assumptions of consistency between direct and indirect evidence from multiple comparisons will be investigated.[89] Where data permit, stratification according to age and disease severity score will be attempted using meta-regression.[90]

6 TAR team expertise

The TAR team at the University of Aberdeen are experienced in conducting reviews of this nature, in both the clinical and technical aspects required to address the commissioning brief. Miriam Brazzelli, Craig Ramsay, Marion Campbell, and Cynthia Fraser have been involved in a number of similar appraisals and the remaining TAR team members are familiar with the methods of systematic reviewing and health technology assessments.

6.1 Team members' contributions

Miriam Brazzelli, Senior Research Fellow at the HSRU, and Craig Ramsay, lead of the Aberdeen Health Technology Assessment Group will oversee and co-ordinate all aspects of the appraisal and be the guarantors of the complete work. Marion Campbell, Director of the HSRU, University of Aberdeen, will provide methodological and content expertise. Moira Cruickshank, Research Fellow at the Health Services Research Unit (HSRU), University of Aberdeen, will be responsible for the day-to-day running of the appraisal and will undertake the review of clinical effectiveness with advice and guidance from Miriam Brazzelli. Cynthia Fraser, Senior Information Specialist at the HSRU, will develop and run the search strategies and will be responsible for obtaining papers and managing references. Graeme MacLennan, Senior Statistician, at the Health Services Research Unit (HSRU), University of Aberdeen, will be responsible for the statistical analyses.

6.2 Advisory group

In addition to the TAR team, an Advisory Group comprising of clinical experts, professionals, and lay members will be set up to provide guidance on current sedation strategies, advise on important outcomes, and assist in the interpretation of the clinical effectiveness findings. The Advisory Group will also consider how to interpret the findings of this assessment in future research recommendations. In particular, issues related to the current state of evidence, appropriate study design, choice of sedative agents, and choice of clinically relevant outcome measures including long-term outcomes will be considered. The Advisory Group will be convened at least twice during the duration of the appraisal. Advisory Group members will include: Anthony Gordon, Director of Research for the Intensive Care Foundation and Clinical Senior Lecturer & Consultant, Critical Care Medicine, Imperial College, London; Bronagh Blackwood, Senior Lecturer, Queen's University Belfast; and two

members of ICUSteps a patients organisation that aims to support people admitted to ICU and their relatives (http://icusteps.org/), together with all the members of the TAR team listed in the previous section.

7 Competing interests of authors

Anthony Gordon has received research grant support from Orion Pharma, the manufacturer of dexmedetomidine. All the remaining authors have no competing interests to declare.

8 Timetable/milestones

Milestone	Date to be completed
Draft protocol	September 2014
Final protocol	October 2014
Assessment report	31 March 2015

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10 Appendices

DRAFT MEDLINE SEARCH STRATEGY

1 Conscious Sedation/

2 exp positive-pressure respiration/

3 exp Critical Care/

4 Critical Illness/

5 (sedation or sedate?).tw.

6 (mechanical adj5 ventilat$).tw.

7 or/1-6

8 Dexmedetomidine/

9 (dexmedetomidine or dexdor or precedex or mpv 1440).tw,rn.

10 8 or 9

11 randomized controlled trial.pt.

12 controlled clinical trial.pt

13 randomi?ed.ab.

14 placebo.ab.

15 drug therapy.fs.

16 randomly.ab.

17 trial.ab.

18 groups.ab.

19 or/11-18

20 exp animals/ not humans/

21 19 not 20

22 7 and 10 and 21