

EVIDENCE-BASED GUIDELINES ON ADULT PROCEDURAL SEDATION AND ANALGESIA

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Abstract

Procedural sedation and analgesia (PSA) has become a popular practice given the high demand for diagnostic screenings and the need to perform invasive procedures offering comfort and pain release. The role and privileges to perform PSA has been debated for years in different guidelines. For this reason, the European Society of Anaesthesiology (ESA) has created a taskforce of expert that has been assigned to create an evidence-based guideline and consensus on the evaluation of patients undergoing PSA, on the role and competences required from the clinician to safely perform these kind of procedures, on the commonly used drugs and the adverse events that PSA can lead and on the minimal requirements to monitor patients and discharge criteria after the end of the procedures. A selection of the current literature from 2003 to 2016 in this specific area was performed by a professional librarian and the retrieved papers were analysed to allow a critical appraisal according the GRADE method. A final total of 2248 papers in the different areas were selected. To obtain the highest level of evidence whenever a topic was not reaching full evidence from the literature, the Rand Appropriateness Method (RAM) with three rounds of Delphi voting was used to obtain a level of consensus between the taskforce experts. This guideline contains recommendations on PSA in the adult population and it is not dedicated to sedation performed in the intensive care unit. The final draft of the document was available for the ESA members through the website for four weeks and to collect all comments. All comments and suggestions were considered and the guidelines were amended accordingly. The ESA guidelines Committee and ESA board finally approved and ratified it before publication.

INTRODUCTION

There has been increased interest in procedural sedation over the last ten years for many reasons, including higher expectations among patients, availability of short-acting drugs, increased numbers of reported major adverse events associated with procedural sedation, and shortage of anaesthetists.

The role of anaesthesiologists in this context has been stated in several guidelines [1, 2] but is still challenged, since some societies and organizations [3, 4] have promoted the use of rapid-acting hypnotic drugs like propofol for procedural sedation by non-anaesthesiologists that had acquired the mandatory skills to manage potentially life-threatening adverse events associated with general anaesthesia or deep levels of sedation induced by these drugs.

Epidemiological data on incidence of adverse events during procedural sedation are controversial. However, the claims analysis of the most common causes of anaesthesia-induced adverse events can be used as an interesting tool, when the inherent limitations of this method are well weighted. For instance, it is impossible to know their true incidence, since the total number of adverse events and the total number of procedures performed are unknown in the claims analysis.

Monitored anaesthesia care (MAC) claims have increased over the last decades – from approximately 2 % of anaesthetic claims in the eighties, to 5 % in the nineties and 10 % in the zeroes. Patient death is the most common clinical outcome in MAC claims, and significantly more common than mortality associated with general or regional anaesthesia [5]. Most fatal incidents result from inadequate oxygenation and/or ventilation in non-operating room areas (NORA) with suboptimal monitoring facilities and ability to prevent and appropriately manage over-sedation.

The *European Society of Anaesthesiology* (ESA) together with the *European Board of Anaesthesiology* (EBA) has created a taskforce with European experts in this field of research and members of both societies. At different stages of this process, its members have determined objectives of the guidelines, criteria for literature search and evidence analysis as well as methods used to provide clinical evidence.

Main objectives of these guidelines are to provide evidence-based consensus on risk stratification for influence of comorbidity on patient outcome, proposed competences to obtain the privilege to provide

procedural sedation, useful hypnotic and analgesic drugs and techniques of administration, patient monitoring, criteria for recovery and discharge, and adverse events.

Definitions

The term “*procedural sedation and analgesia*” (PSA) [6] involves the use of short-acting hypnotic and/or analgesic medications to enable clinicians to perform diagnostic or therapeutic procedures effectively, while monitoring the patient closely for potential adverse effects. This procedure was previously (and inappropriately) termed *conscious sedation*, although effective sedation reduces consciousness. Appropriate procedural sedation results in preserved airway control and spontaneous respiration despite depressed levels of consciousness.

Sedation and analgesia introduce independent risks of morbidity and mortality in addition to the procedure itself. By recognizing those risks, the *Joint Commission on Accreditation of Healthcare Organizations* (JCAHO) mandates sedation practice throughout any institution in the USA to be monitored and evaluated by a Department of Anaesthesia, not required to be directly responsible of sedation services, privileging, or quality assurance, but rather to have an advisory and supportive role [7].

There are different recognized ways to define and assess various levels of sedation. The original one is a modified version of the five-level *Ramsay* scale [8], where level 5 is similar to, or synonymous with, general anaesthesia:

Level 1: Fully awake.

Level 2: Drowsy.

Level 3: Apparently asleep but arousable by normal speech.

Level 4: Apparently asleep but responding to standardized physical stimuli (e.g. glabellar tap).

Level 5: Asleep, but not responding to physical stimuli (comatose).

The *American Society of Anesthesiologists* (ASA) has defined four levels of sedation [9], where level 4 corresponds to general anaesthesia:

Minimal sedation: Normal responses to verbal stimuli. Cognitive function and coordination may be impaired. Ventilatory and cardiovascular functions are unaffected.

Moderate sedation: Purposeful responses to verbal/tactile stimuli and verbal commands. Airway is patent, and spontaneous ventilation is adequate. Cardiovascular function is usually unaffected.

Deep sedation: Not easily arousable. Purposeful responses to repeated verbal/tactile or painful stimuli. Ability to maintain a patent airway and spontaneous ventilation may be impaired. Airway and/or respiratory support may be required. Cardiovascular function is usually unaffected.

General anaesthesia: Not arousable. No response to painful stimulation. Ability to maintain a patent airway and spontaneous ventilation is impaired. Airway and respiratory support is required, and positive pressure ventilation may be required. Cardiovascular function may be impaired.

Although differences between levels of sedation are not clear cut, whenever a patient reaches a lower level of consciousness, there is also higher risk of life-threatening adverse events calling for immediate and appropriate bedside management. For that reason, the *Centre for Medicaid and Medicare Services* (CMS) has published the Revised Hospital Anaesthesia Services Interpretive Guidelines – State Operations Manual [10], where deep sedation is part of MAC. These guidelines apply to all procedures where anaesthetists provide specific anaesthesia services in patients undergoing elective diagnostic or therapeutic procedures, also under local anaesthesia or, in some cases, no anaesthesia at all. Any provider of MAC must be prepared and able to rapidly and appropriately convert to general anaesthesia, and to support airway and/or respiratory function, whenever necessary. MAC is mainly PSA when provided by an anaesthesiologist.

METHODS

LITERATURE RETRIEVAL

A taskforce was created to develop European guidelines on procedural sedation based on clinical and scientific expertise in this area. Different subcommittees constituted this taskforce: Selection of patients, competences required, drugs and adverse effects, monitoring, recovery, and discharge.

With the final text in perspective, a set of questions and keywords was prepared by the taskforce to guide a literature search. These were first drafted by each subcommittee and then validated by the chairmen of the taskforce and literature reviewers. The taskforce members also established inclusion/exclusion

criteria for the studies. This process was completed by November 2013. The final literature search was done in January 2014 and then updated in June 2016. A broad filter for procedural sedation was applied in conjunction with a study type filter and a specific subgroup filter based on the questions and keywords. The MEDLINE, EMBASE, and Cochrane Library databases were searched from 2003 to December 2013 for the normalized and free-text terms “(conscious sedation)”, “(deep sedation)”, “procedure*” “intervention*” or “exam*” according to the Appendix. A total of 12,263 records were identified. Original articles identified this way went through a two-round selection process.

Screening of the first title and abstract was done to remove duplicates and select papers according to inclusion criteria of the study. This process was carried out by a systematic reviewer and when in doubt checked by a second one. Systematic reviews, randomized controlled trials, cohort studies, case control studies, and cross sectional surveys were included. Existing guidelines were identified and considered separately. Narrative reviews, editorials, case series or case reports were excluded. Only English language papers were included. A total of 2,248 papers were selected.

A second sift was done by each subcommittee to identify papers on adults (older than 18 years) receiving sedation for any painful or non-painful diagnostic or therapeutic procedures, excluding dental surgery and other minor operations carried out under local anaesthesia. Articles covering long-term sedation in critical care, other than for specific procedures, were also excluded. The expertise of each subcommittee members guided their selection. As we wished to include all relevant papers, the subcommittees included any paper considered potentially relevant and also suggested papers for appreciation by other subcommittees. After this two-round selection, 482 full-text papers had been made available for taskforce. The articles were individually checked for risk of bias, applicability and clinical significance. Studies where the intervention was obsolete were excluded.

Once the final number of papers had been set, evidence gathered was critically appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]. As GRADE was used to assess the quality of evidence, the following features were assessed for each outcome. GRADE was based on limitations of study design (selection, performance, detection, attrition and reporting of bias), effect consistency and size, directness, precision, publication bias, dose-response effect, and presence of antagonistic bias. The transformation

of evidence into a recommendation was a function of the panel evaluation of the five factors summarized in Section C of Table 1. Since the GRADE system could not be used to standardize the decision-making process of the expert panel, the methodology committee of this working group selected the Rand Appropriateness Method (RAM), published in detail elsewhere [24, 25], for that purpose.

For consensus, where strong evidence was lacking, a three-round Delphi method was used. The expert panel met in Berlin in June 2015 for a first round of anonymous voting after face-to-face debating. The second and third voting rounds were both internet-based. The experts formulated draft recommendations before each process of voting to serve as a foundation for subsequent discussion and evaluation. The expert panel was updated by short presentations of the literature search results and subsequent interpretation for drafting of the proposed recommendations. The voting process included expert judgments on GRADE factors, such as outcome, importance and evidence-to-recommendation transformers summarized in Table 1 (Section C) and Table 3. The algorithm in Figure 1 depicts the final rendering of disagreement/agreement graded by the degrees of agreement. This process provided a structured and validated method for expert panel activities. In addition, it standardized statistical methodology for determining the degree of agreement to serve as a foundation for deciding about the recommendation grade (strong versus weak).

RESULTS

RISK STRATIFICATION FOR INFLUENCE OF COMORBIDITY ON PATIENT OUTCOME

Appropriate pre-operative evaluation should be done in cardiac patients undergoing procedural sedation, and an anaesthesiologist should be involved in patients with severe cardiovascular comorbidity (Strong consensus - Level of evidence A- GoR A).

Patients with cardiac problems should be carefully evaluated and optimized according to a “*primum non nocere*” strategy. This involves full evaluation of cardiac physical status and cardiac reserve [26] also before procedural sedation. In emergency procedures (e.g. gastroscopy for bleeding), this evaluation might have to be limited. In all other cases, a more complex and systematic approach should be

considered, including patient history and co-morbidity, physical examination including blood pressure measurement and pulmonary auscultation, biochemical testing, electrocardiography (ECG) at rest, and echocardiography, since urgency, invasiveness and persistence of those procedures, particularly under suboptimal conditions of sedation and analgesia, can elicit stress responses with myocardial ischaemia, impairment, and failure in cardiac patients [27, 28]. Predictive models for pre-operative assessment of cardiac risk factors [29, 30] may provide objective clinical tools for assessing and predicting individual risks of cardiac events also in patients undergoing non-cardiac procedures under PSA. Cardiac patients may also require procedural sedation for minor or major cardiac procedures like left heart catheterization or coronary stenting [31, 32], electrical cardioversion [33], and implantation of internal defibrillators [34], pacemakers or trans femoral aortic valves [35]. Current practice for these procedures is to provide PSA with benzodiazepine (mainly midazolam) and/or propofol, and low-dose opioid [32, 35]. Dexmedetomidine has been proposed as an adjuvant, but its use has been reported mainly in paediatric patients and it is currently off-label [36, 37]. The essential role of an anaesthetist has been previously advocated in patients with moderate to severe hypotension (systolic blood pressure < 90 mmHg) or major cardiac dysfunction [38, 39].

Patients with obstructive sleep apnoea should be carefully evaluated before procedural sedation, and an anaesthesiologist should be involved in high-risk patients (Strong consensus - Level of evidence B- GoR A).

Patients with obstructive sleep apnoea syndrome (OSAS) are more vulnerable to drug-induced cardiopulmonary depression during deep sedation [40]. There are different validated instruments to identify patients at risk of OSAS, like the Berlin [41] or STOP-BANG [42] questionnaires. Although the use of “conscious sedation” in OSAS patients did not seem to be related with major and minor cardiopulmonary adverse events [43, 44, 45, 46] when the procedure was performed by a non-anaesthesiologist, these data are of limited evidence given their retrospective evaluation. The presence of OSAS does not *per se* predict cardiopulmonary complications [46]. However, procedural sedation in OSAS patients often requires deeper levels of sedation or even general anaesthesia. Hypoxaemia, hypotension, or premature termination of the procedure may occur also with anaesthesiologists providing

MAC of OSAS patients [47] and requires professional skills to be rapidly and appropriately managed. Pre-operative recognition of OSAS is an essential first step in preventing and managing potential complications. A thorough patient history (e.g. snoring, witnessed apnoeas during sleep) and physical examination are important in raising a suspicion of OSAS, but the absence of typical clinical features does not exclude OSAS.

Management of OSAS patients undergoing procedural sedation requires thorough and appropriate understanding of different pharmacological options available, where minimal doses of hypnotics should be used and opioids avoided. Dexmedetomidine has a good safety profile and should be considered as an alternative choice for sedation [48]. In patients with severe OSAS, the use of nasal continuous positive pressure might reduce risks of post-procedural respiratory complications [49].

An anaesthesiologist should be involved in procedural sedation in morbidly obese patients (Strong consensus – Level of evidence A- GoR A).

Morbidly obese patients are at higher risk of respiratory complications during procedural sedation for several reasons, including impaired function of respiratory muscles, reduced functional residual capacity, and limitation of expiratory flow [50, 51, 52], increased oxygen consumption, increased production of carbon dioxide and increased work of breathing at rest [50], increased upper airway resistance with propensity for OSAS [53, 50, 51, 52], and potential for obesity–hypoventilation syndrome, followed by pulmonary hypertension and right heart failure [54, 55]. Although being a robust and simple clinical tool for assessment of obesity, the BMI does have its limitations, and e.g. heavily muscled individuals are classified as being overweight. It is now believed that other factors, such as young age and pattern of adipose tissue distribution, may be better predictors of health risk, and the waist height/hip ratio is also considered to be more predictive in obesity [56]. In particular, central obesity seems to be more related to increased impairment of breathing, which is often enhanced during sedation. Since obese patients with OSAS are more prone to obstructive breathing, use of the Berlin [41] or STOP BANG [57, 47] questionnaires is proposed to assess the severity of OSAS before providing sedation in these patients.

Practical suggestions whenever sedation is to be carried out in obese patients are to avoid the supine position and place the patient in a beach chair position, prefer endotracheal intubation as the default

choice of airway management, avoid long-acting sedatives, avoid drugs with respiratory depressant effects on the breathing frequency and/or depth, and avoid drugs that induce or reinforce obstructive breathing in non-intubated patients. Propofol for sedation seems to be associated with respiratory complications also when used by anaesthetists, and remifentanyl and dexmedetomidine (as off-label use) have hence been proposed for tailored titration of sedation and analgesia with appropriate bedside monitoring of breathing and depth of anaesthesia [58, 59].

Patients with chronic renal failure have higher risk of developing respiratory problems during procedural sedation, and appropriate care and monitoring is required (Strong consensus – Level of evidence B- GoR B).

Procedural sedation and analgesia is required to relieve anxiety and minimize discomfort associated with arteriovenous fistula formation and other procedures in chronic renal failure (CRF) patients. Propofol and alfentanil used to achieve a similar degree of sedation and analgesia have been reported to induce more oxygen desaturation and apnoea/hypoventilation in CRF patients than in control patients [60]. PSA during procedures of vascular access for haemodialysis, intravenous (i.v.) administration of drugs with rapid onset and short duration of action, like midazolam and/or fentanyl, are generally preferred. No difference has been reported in distribution, elimination, or clearance of unbound midazolam between normal subjects and CRF patients given i.v. doses of 0.2 mg/kg [61]. As for midazolam, rapid onset and short duration of action make fentanyl an ideal drug to use in this setting. The pharmacokinetics of single-dose fentanyl are not affected in CRF [62, 63, 64]. Like midazolam [65], fentanyl is primarily metabolized by the liver [66]. Major, mainly cardiovascular and/or pulmonary, adverse effects associated with the administration of either midazolam or fentanyl have been reported to increase when the two drugs are being combined [67], particularly in high-risk CRF patients, and there is need for careful intra- and post-procedural respiratory monitoring and management of these patients.

Careful evaluation and choice of drugs for procedural sedation is recommended in patients with chronic hepatic disease (Strong consensus – Level of evidence A-GoR A).

Patients with chronic liver disease are often exposed to endoscopic procedures requiring sedation for diagnostic assessment of e.g. oesophageal varices or portal hypertensive gastropathy. Hepatic dysfunction resulting from liver disease can significantly change metabolism and pharmacokinetic properties of hypnotic drugs. The risk of complications related to sedation is increased in these patients [68, 69]. Midazolam is preferred in most centres because of rapid onset and potent amnestic properties. However, prolonged plasma half-life may increase the risks of adverse effects in hepatic dysfunction [70, 71, 72, 73].

In minimal hepatic encephalopathy (MHE), procedural sedation with midazolam caused exacerbation of symptoms for up to two hours after the end of the procedure [74, 75]. Propofol used for sedation has a more favourable pharmacokinetic profile requiring no dose adjustment in renal or hepatic failure. Propofol sedation in chronic hepatic failure (including Child C patients) has been reported to be superior to midazolam sedation in terms of safety, efficacy and recovery [76, 77, 78, 79, 80, 81, 82, 83]. Propofol-induced desaturation is not common in hepatic failure but can occur requiring supplemental oxygen and airway support. Oxygen saturation measurement before PSA can help detecting a hepatopulmonary syndrome [76, 84].

Comprehensive evaluation, including ability to provide informed consent, is required before procedural sedation in elderly patients (Strong consensus - Level of evidence A- GoR A).

There are many age-related physiological changes in the cardiac, pulmonary, renal, hepatic, endocrine, and nervous systems in elderly patients that need to be evaluated to determine if those patients are at increased risk for procedural sedation [85, 86]. Studies suggest that there are increased risks of hypotension, hypoxaemia, cardiac arrhythmias, and aspiration in elderly patients undergoing procedural sedation compared with younger patients [87, 88, 89].

Endoscopic procedures are generally safe in elderly patients, with complication rates similar to those in younger patients [90, 91, 92, 93, 94, 95]. An exception is colonoscopy, which is associated with higher perforation rates in patients over 65 years and with higher rates of cardiovascular, pulmonary, and total complications in patients over 80 years compared with younger patients [96, 97, 98]. For long procedures, like endoscopic retrograde cholangiopancreatography (ERCP), different sedative drugs have been used,

and the main concerns seems to be related to reduced doses to avoid over dosage, post-procedural desaturation, and prolonged recovery [99, 100].

It is well known that essential pharmacokinetic and pharmacodynamic changes are associated with the process of ageing. Apparently, the brain becomes more sensitive to hypnotic drugs with age [101]. By evaluating specific effects of propofol by electroencephalography (EEG), Schnider et al. have demonstrated increased sensitivity to propofol in elderly patients [102]. An appropriate dose reduction for midazolam and propofol for endoscopies in elderly patients has been extensively studied [103, 104, 105]. The onset of action of all anaesthetic drugs used in elderly patients is much slower and the speed of dose-titration should be adapted accordingly.

There is increased risk of adverse events associated with procedural sedation in high-risk (American Society of Anaesthesiologists (ASA) classes III-IV) patients and those older than 60 years (Strong consensus – Level of evidence B- GoR A).

High-risk (ASA class 3 or higher) patients and those above 60 years of age, undergoing procedural sedation have higher risk of hypoxaemia due to hypoventilation [106, 107, 108], calling for close bedside observation, monitoring, and management of airway patency and respiration. A new tool to assess potential risk related to procedural sedation called the area under the oxygen saturation curve (AUCDesat) has been advocated as an useful predictive composite index for sedation risk assessment, reflecting individual duration and extent of desaturation over time [109]. Its clinical role needs to be validated in outcome studies.

The upper airways should be assessed before procedural sedation (Strong consensus – Level of evidence B- GoR B).

Assessment and documentation of the upper airways should be done before any procedural sedation. Methods of systematic airway examination have been designed to identify patients where ventilation by face mask [110, 111, 112] and/or endotracheal intubation [113, 114, 115, 116, 117] might be difficult with standard techniques, but all difficult airways cannot be predicted [115].

Difficult upper airways are associated with, but not exclusively limited to, individual deviations in general habitus (significant obesity, pregnancy) [118, 119, 120, 121], head and neck anatomy (short thyromental distance, limited cervical range of motion, facial or neck trauma, tumour, oedema, abscess, haematoma, tracheal deviation, large neck circumference, dysmorphic facial features, excessive facial hair), mouth opening (small mouth opening, trismus, macroglossia, protruding incisors, small inter-incisor distance, toothlessness, tonsillar hypertrophy, high arched palate), and jaw anatomy (micrognathia, retrognathia, inability to prognath) [115]. For more details, we refer to current reference literature of anaesthesiology.

PROPOSED COMPETENCES AND ENVIRONMENT FOR PRIVILEGING PROCEDURAL SEDATION

Besides environmental factors (e.g. locations of procedural and recovery sites, room sizes, spatial logistics, and equipment), human and procedural factors (e.g. staff qualification, guidelines, emergency support) do also influence patient safety. A basic rule for safe procedural sedation is that the person performing the sedation should be only responsible for it: doing altogether the procedure and the sedation is unsafe.

STAFF

All staff dealing with patients undergoing procedural sedation should be certified with an advanced life support course (e.g., ERC or AHA). The provider in charge of PSA cannot be the same performing the procedure (Strong consensus – Level of evidence B; GoR A).

The risk of complications and emergency situations during or after procedural sedation is increased if staff is inexperienced and less trained. Complication rates in low-risk patients are considered to be lower than in high-risk patients.

The main problems encountered in patients during and after procedural sedation include hypoxia/desaturation (40.2%), vomiting/aspiration (17.4%), hypotension/haemodynamic instability (15.2%), apnoea (12.4%), and possibly cardiac arrest. Although some complications are non-fatal, they

can easily lead to cardiac arrest requiring cardiopulmonary resuscitation (CPR) [122]. Therefore, proper emergency training of all staff caring for patients during or after procedural sedation is crucial. Training should include not only management of cardiac arrest but also prevention, recognition of a deteriorating situation and management of deterioration early in the course.

Being able to perform CPR immediately in the case of cardiac arrest also requires specific medical material, including defibrillator, to be immediately available wherever procedural sedation takes place. This should be emphasized. The sentence was moved from the section on airway management below.

Scenario- and simulation-based training in endoscopic haemostasis may provide opportunities to improve procedural skills and acquire practical experience in managing this medical emergency, which also requires the ability as a team leader to rapidly process, integrate, and appropriately respond to complex information under emergency conditions [123]. However, sole manikin training has been shown not to result in sufficient improvement of skills for patients [124]. This underlines the importance of a specific attention to the science of human factors.

Minimal requirements for provision of procedural sedation include ability to appropriately perform pre-procedural clinical assessments (including upper airways and comorbidity), competence of intravenous cannulation, appropriate skills for rapid assessment (by direct bedside observation and clinical monitoring) and management of different levels of sedation, airway patency, and respiratory and haemodynamic depression, detailed knowledge of drugs used for sedation and emergency management, certified competence of advanced life support and proper monitoring of the patient (Strong consensus, Level of Evidence B-GoR A).

There is consensus in the literature on needs for certified training of staff directly involved in procedural sedation [1, 125, 126, 127, 128, 129, 130]. According to the Academy of Royal Colleges, individuals who administer sedative drugs should be aware of possible adverse events and be prepared and able to rapidly recognize and manage them [131]. Therefore, this taskforce agrees that each sedationist should be able to evaluate and manage various degrees of consciousness. There are currently different sedation scores that can be used but the main ones are the Ramsay sedation score and the University of Michigan Sedation Scale [132, 133].

The person in charge of the procedural sedation/analgesia has to be competent in detecting and managing respiratory (or haemodynamic) depression at early stages. He/she should undergo an appropriate theoretical training to induce and maintain the loss of consciousness including: drugs commonly used for sedation, pre-operative assessment of patients (including airways), monitoring of the patient during the procedure, how to respond to the major emergencies during sedation (anaphylaxis, over sedation, airway obstruction, cardiac arrest). The theoretical training should be assessed by a written formal exam with multiple choice questions with a minimal passing score of 75% [125].

Practical skills mandatory to achieve competence in delivering a safe sedation should include at least bag mask ventilation and placement of a supraglottic airway. Intubation should not be a mandatory requirement but in case there is the need for it, there is evidence that intubation performed by non-anaesthetist is one of the predicting factors for difficult intubation [134] and there is need for a certain number of successful intubation before considering the trainee proficient in airway management [135, 136]. Given the possibility of having major adverse effects during sedation even in healthy patients [137], it is suggested to have a certified competence in advanced life support in all personnel involved in the procedural sedation. Another foundation of the training is the recovery from unconsciousness. The responsible for providing procedural sedation/analgesia should be competent in recognition of full recovery of consciousness [1] using objective tools [138, 132] and in case of prolonged or unexpected over sedation there should be a specific protocol to be followed to keep patient's vital signs stable [139].

Training completion should be validated according a Global Rating Score (GRS) previously used in other settings [140, 141] that could certify the competence of the trainee dedicated to provide procedural sedation and allow to give different privileges according the standard achieved during the final evaluation. This Taskforce suggests that a GRS for evaluating procedural sedation acknowledgments and skills should be used before giving privileges for procedural sedation to non-anaesthetists (appendix GRS).

INFORMED CONSENT

The clinician has to discuss the risk, benefits and techniques to deliver PSA with the patient before performing the procedure (strong consensus, Level of evidence B, GoR A).

Before performing PSA, the clinician has to complete a full clinical evaluation of the patient in order to discuss the potential harms and the suggested plan for the scheduled procedure. The clinician should also disclose/present potential alternatives of the procedure (in case of failure) that could also include not having any treatment. The legal concept of the reasonable person is used in obtaining informed consent. The reasonable person doctrine centres on material risks. Material risks is one that the provider knows or ought to know would be significant to a reasonable person in the patients' position of deciding whether to submit to a particular medication or treatment procedure. However, all conceivable risks do not require disclosure. A printed informed consent form should be used and the informed consent needs to be witnessed. Consent from waivers can be considered acceptable wherever the patient is unable to provide explicit consent due to severe pain or altered mental status [142, 143, 144].

MATERIALS

A difficult airway cart should be readily available wherever procedural sedation takes place (Strong consensus – Level of evidence B - GoR A).

The initial sentence on material for CPR has been moved to the section on CPR above. Since airway problems during sedation are quite common and may rapidly lead to severe hypoxia, an approved algorithm for difficult airway management should be readily available. If no difficult airway chart is available, specific pre-packed material, e.g. in bags, may be adequate for immediate supply in case of emergency [145, 146].

ENVIRONMENT

A code blue button installed in the procedural sedation room can facilitate an alarm in case of emergency (Strong consensus – Level of evidence C - GoR C).

A code blue button installed in the procedural sedation room can facilitate alarming in case of emergency, an immediate and appropriate response is vital. However, there are different ways to facilitate alarming of

emergency teams for help. Having a code blue button, or at least specific and well-known alarm procedures, may save patient lives in emergency situations [145].

HYPNOTIC AND ANALGESIC DRUGS AND TECHNIQUES OF ADMINISTRATION

It is beyond the scope of these guidelines to review in detail the pharmacology of sedative and analgesic drugs commonly used to provide adequate comfort to patients subjected to diagnostic or therapeutic procedures and previously described elsewhere [147, 148, 149]. Instead, the main goal of this taskforce in this context is to focus on basic pharmacokinetic and pharmacodynamic aspects of sedative and analgesic drugs. To ensure safe drug administration, clinicians should always be aware of the pharmacological properties of each drug and drug combinations used [67].

Drug selection for PSA should be based on easiness of dosing in order to reach and maintain the desired level of sedation and analgesia hereby avoiding adverse events caused by excessive dosage or unexpected reactions to the drug itself or the combination of them. As such, the theoretically ideal drug for PSA has a rapid onset, short duration of action and time-independent context-sensitive half-time. Additionally, it should have a beneficial hemodynamic and respiratory stability profile. As most of the available drugs for PSA doesn't covers both the hypnotic and analgesic endpoints, drug combinations are mostly required [150]. Hereby, the clinical should understand the principles of drug interactions to balance between clinical effects and side-effects [151, 152].

For most of the applied drugs, the recommended route of administration during PSA is intravenously as the pharmacokinetic effect can be better predicted [147]. Some upcoming evidence exists on intranasal drug administration during PSA, e.g. for dexmedetomidine [153].

Propofol remains the most common sedative drug [154, 155, 156, 157, 158, 159, 160], mainly for its short onset time (30-60 s) and predictable duration of action and short context-sensitive half-time. It induces a dose-dependent amnesia and sedation, leading to unconsciousness and general anaesthesia at higher concentrations [161]. As propofol has no analgesic properties, it is mostly combined with opioids during PSA resulting in a strong synergistic relationship of both sedative and analgesic effects. Additionally, these drug combinations can induce significant hemodynamic and respiratory instability requiring fine-

tuned titration [162, 163]. Alternatively, ketamine and dexmedetomidine has been described as adjuvant drugs with propofol. Pain at the site of injection is a problem which can be minimized reducing the concentration to 0.5% or administering lidocaine or opioids intravenously before its administration.

Benzodiazepines are still used for procedural sedations. The main drug used is midazolam for its rapid onset (30-60 s) and the maximum effect is reached after 5-7 min. Its duration of action is longer than propofol (20–80 min) and with a prolonged half-life, for this reason, it is used mainly for shorter procedures but with caution in elderly patients or patients with comorbidities [164, 165]. As midazolam has no analgesic properties, it is typically combined with opioids during PSA.

Ketamine differs from other sedatives in several ways. It possesses analgesic properties and can, therefore, be used as the sole agent for painful procedures. It has a rapid onset of action (30–60 s) and the moderate duration of action (10–20 min). Because of the cardiovascular stimulation ketamine should be used cautiously in patients with ischemic heart disease [166, 167].

Two α 2-agonists (clonidine and dexmedetomidine) are used for sedation in clinical practice. While clonidine has a long duration of action as it's highly lipophilic, dexmedetomidine is more plasma protein binded [168]. Dexmedetomidine needs to be administered by a slow initial bolus followed by continuous infusion. Its use as 'per se' sedative drug or combined with opioids has recently reached great success in paediatric patients even if the recommended use is for continuous sedation in patients admitted in the intensive care unit [169]. Dexmedetomidine has a beneficial respiratory stability profiles, however, caution is required as cardiovascular changes related to speed of injection are present [170].

Different opioids are often used to relief pain during procedures. Although morphine is the reference drug, synthetic opioids such as fentanyl, alfentanil, sufentanil, and remifentanil are more useful to supplement sedatives for short painful procedures.

Most drugs during PSA are injected as single or repeated boluses or as a continuous infusion. For propofol and remifentanil, pharmacokinetic-based, target-controlled infusion has been introduced in clinical routine and proven to outstand manual infusion schemes, resulting in fewer episodes of apnoea, better hemodynamic stability, better patient and clinician satisfaction, better monitoring focus and better patient recovery [171, 172].

STANDARD MONITORING AND SETTING FOR PROCEDURAL SEDATION/ANALGESIA

Continuous visual bedside observation of the patient represents the basic level of clinical monitoring during and after any procedural sedation (Strong consensus - Level of evidence B - GoR B).

Given the rapid changes caused by the administration of sedative medications combined with analgesic drugs, it is important to have a continuous assessment of the levels of sedation that can vary during the procedure. This requires vigilance on the patient, ongoing assessment and documentation [173, 174]. The depth of sedation should be assessed periodically throughout a procedure by utilizing one of these scales or by assessing responsiveness to verbal and tactile stimulation [175, 176, 133]. During procedures where a verbal response is not possible (e.g., oral surgery, upper endoscopy), the patient has to demonstrate his/her level of consciousness as squeezing the hand when he/she is stimulated through verbal or tactile. This response suggests that the patient will be able to control his airway and take deep breaths if necessary, corresponding to a state of moderate sedation. Note that a response limited to reflex withdrawal from a painful stimulus is not considered a purposeful response and thus represents a state of deep sedation or general anaesthesia.

Intermittent non-invasive measurements of blood pressure and continuous electrocardiography (ECG) monitoring are considered mandatory in all patients undergoing procedural sedation (Strong consensus – Level of evidence B - GoR A).

Intermittent frequent measurements of non-invasive blood pressure (NIBP) at least every 5 minutes although such monitoring could interfere with the procedure (ref ASA) and continuous electrocardiography (ECG) monitoring are both considered mandatory in procedural sedation. This statement is supported by the working group and non-RCT publications [177]. The importance of monitoring these parameters is supported by the fact that significant hypoxia and cardiac arrhythmias have been reported to be associated with upper gastrointestinal endoscopy with or without sedation. Nevertheless, those events have been proposed to be associated with age and comorbidity of the patient, the extent and duration of the procedure, and experience of the endoscopist [178]. Pulse rate and systolic

blood pressure have also both been reported to increase on pharyngeal introduction of an endoscope [179].

Pulse oximetry – the most important device for clinical bedside monitoring – should be used in all patients undergoing procedural sedation (Strong consensus – Level of evidence B - GoR A).

As already mentioned above, continuous bedside observation of the patient should be the basic level of clinical monitoring in any patient subjected to procedural sedation. Pulse oximetry, providing transcutaneous values of haemoglobin oxygenation (SpO_2), should be used as a minimum standard for continuous monitoring of all patients undergoing procedural sedation. Not using pulse oximetry to monitor sedation cannot be considered ethically acceptable. Continuous supply of oxygen and monitoring with pulse oximetry are mandatory to minimize the risk of, and rapidly manage, hypoxaemia [180, 181]. Today, pulse oximetry is the standard of choice for bedside monitoring of severely ill or injured patients in perioperative, intensive care and emergency medicine [182, 183]. Pulse oximetry enhances patient safety by detecting hypoxaemia earlier and more reliably than other methods [182, 184]. The sites most commonly used for detection (finger, toe, ear) have similar accuracy [183]. If available, the variable pitch “beep,” which gives a continuous audible indication of the oxygen saturation reading, may be helpful.

It is recommended to measure SpO_2 before starting procedural sedation, when the patient is breathing room air, in order to know the patient’s baseline SpO_2 and to know which value should be targeted for during the recovery period

However, when using pulse oximetry, it should be taken into account that some influencing factors may lead to false measurements or a delayed display of desaturation or resaturation. Changes in measurement kinetics or perfusion can lead to aberration of the pulse wave signal with deviations in accuracy and precision [185, 184], e.g. in hypotension [185], or when nail polish [186] or acrylic finger nails [187] are used.

Pulse oximetry (SpO_2) measures oxygenation only but not alveolar ventilation once supplemental oxygen is given to the patient [180]. Therefore, additional monitoring should be used to ensure appropriate respiratory function.

Capnography – by facilitating early detection of ventilation problems – should be used in all patients undergoing procedural sedation (Strong consensus – Level of evidence A - GoR A).

In addition to continuous monitoring by visual observation, NIBP, ECG and pulse oximetry, capnography should be used for continuous evaluation of ventilation [180]. It monitors the end-tidal concentration of carbon dioxide, which is in theory more sensitive to alveolar hypoventilation than SpO₂, and is standard monitoring of endotracheal intubation and ventilation in general anaesthesia [180, 188]. Sidestream capnography can be measured with special nasal cannulae. Capnography has also been shown to provide earlier indications of apnoea than pulse oximetry [180, 189].

Other studies have shown interventions based on capnography compared with standard monitoring with a pulse oximeter result in decreased episodes of apnoea and hypoxaemia [190, 191, 192]. Capnography detected 54 episodes of apnoea, and pulse oximetry 27 of them, in 28 of 49 patients subjected to procedural sedation for upper gastrointestinal endoscopy [189]. The addition of capnography to standard monitoring for propofol sedation in adult emergency care reduced, and improved early detection of, hypoxic events [193]. Simultaneous use of other techniques for carbon dioxide measurement (arterial blood gas analysis, transcutaneous measurement) can enhance the validity of capnographic measurements [194].

A recent meta-analysis [195] supported the use of capnography during PSA concluding that episodes of respiratory depression were 17.6-times more likely to be detected by capnography compared with standard monitoring.

Given this evidence in the literature ASA and the Academy of Medical Royal Colleges included capnography in the basic monitoring standards whenever the patient has to undergo moderate or deep sedation [196, 173].

USE OF SUPPLEMENTAL OXYGEN

Supplemental oxygen should be available whenever PSA is started and it could be administered to prevent hypoxia, especially in long procedures or whenever an hypoxic period is anticipated(strong Consensus- Level of evidence B - GoR B)

The literature is still debating on the use of supplemental oxygen during PSA [197, 198, 199] to reduce the incidence of hypoxemia. The best evidence supporting the use of oxygen is a double blind, randomized trial of adults undergoing PSA with propofol [197] in which episodes of hypoxia (SpO₂ <93 percent) lasting longer than 15 seconds occurred significantly more often (41 percent) among the 58 patients given compressed air by face mask compared to the 59 patients given high flow oxygen (19 percent) using the same delivery system (difference 23 percent; 95 percent CI 6-38 %). However, the clinical significance of such transient episodes of hypoxia remains debatable.

Several observational studies have found that supplemental oxygen at lower concentrations does not reliably prevent hypoxemia during PSA [200, 201] and delays the detection of respiratory depression in patients without EtCO₂ monitors, since SpO₂ levels may not fall until a prolonged period of hypoventilation or apnoea has occurred [202, 203].

PROCESSED ELECTROENCEPHALOGRAM (pEEG) MONITORS

pEEG monitors should be used for monitoring of procedural sedation – particularly when using propofol (Strong consensus – Level of evidence B - GoR B)

BIS monitoring has been reported to minimize complications during sedation and to evaluate by objective measures the level of sedation [204, 205]. Additional BIS monitoring has been reported not to improve oxygenation or reduce cardiopulmonary complications [206], and no clinical role of this kind of monitoring has been found during sedation for endoscopic procedures [207]. Nevertheless, BIS monitoring during procedural sedation with propofol has been reported to be associated with higher satisfaction among patients and endoscopists [207, 208], and to enable more effective titration and shorter procedures of sedation [209]. Altogether, available results on the use of BIS monitoring for procedural sedation remain controversial.

Clinical data on other cerebral monitoring methods (e.g., spectral entropy or Narcotrend™) is rare. The scarce results indicate that they can be utilized as monitor mainly to determine the depth of sedation during a propofol-based sedation [210]. Clinical assessment and Narcotrend™-guided sedation using propofol for deep sedation demonstrated comparable propofol dose and recovery time [211]. Both

monitoring systems were equally safe and effective. However, the Narcotrend™-guided sedation showed less hemodynamic changes and fewer complications compared with the clinical assessment-guided sedation [211]. Evidence supporting the use of these devices during PSA is supported by a limited number of studies.

RECOVERY AND DISCHARGE AFTER PROCEDURAL SEDATION/ANALGESIA

Patients must be monitored in a recovery room for at least 30 minutes after procedural sedation (Strong consensus – Level of evidence B - GoR B).

Since patients may deteriorate considerably after procedural sedation, sufficient monitoring is essential, but there is no clear evidence on the way they should be monitored after procedural sedation. Although there is no clear evidence on who should monitor patients and how long patients should be monitored, from a practical point of view, post-sedation monitoring (with at least NIBP, ECG, and pulse oximetry) is essential to supplement continuous visual observation by an experienced trained nurse. No clear recommendation can be given on whether recovery should take place in a separate room or in the sedation area, but monitoring for at least 30 minutes after procedural sedation is considered to be adequate [212].

The basic endpoints criteria to consider the patient dischargeable after PSA can be the following:

- Low risk procedure with no need to monitor postoperative complications
- Mental status and physiological signs should be returned to the baseline values and patients should be able to take care of him/herself or just with minimal help
- Postoperative symptoms as pain, nausea, dizziness should be well tolerated
- A reliable person should be always present with the patient to help him/her in the first hours after discharge.

Discharge criteria should be designed to minimize the risk for cardiorespiratory depression after patients are released from observation by trained personnel. Some discharge scores have been used successfully before to assess the patient after PSA and allow for an earlier discharge after colonoscopy [213, 214]. It has also been suggested that patients are ready for discharge when they have reached their

"neuromuscular and cognitive pre-procedure baseline" [212]. To check discharge criteria in patients after PSA, the ALDRETE score seems to be feasible [215].

Clear written discharge instructions should be given to the patient and to the patient's caregiver. The clinician discharging the patient needs to explain the postoperative plan, which problems can arise and how to solve them and when the patient can return to normal activity. A follow-up should be offered to the patient in case he/she could experience problems after having been discharged home.

ADVERSE EVENTS RELATED TO PROCEDURAL SEDATION/ANALGESIA

Procedural sedation analgesia (PSA) can be the cause of a wide range of complications that can happen during or after the procedure. These range from mild to life-threatening events that need proper recognition and management by the clinician involved in the administration of the PSA.

(Strong consensus- Level of evidence B, GoR A).

Even best practice may result in unavoidable complications not being able to avoid. Relevant problems after PSA [216, 217, 218, 219, 220, 221, 222, 223, 89, 224] include the following but may not be limited to:

Major problems as:

- Respiratory depression may present as a decrease in depth and/or rate of ventilation and is attributed to depression of respiratory control centres, which normally trigger breathing as carbon dioxide levels in the blood rise slightly above the normal threshold. All sedatives, opioids, and potent general anaesthesia inhalation agents have the potential to depress central hypercapnic and/or peripheral hypoxemic drives, but this risk is minimal with moderate sedation, provided one uses conventional doses and monitors the patient appropriately. Nevertheless, one must be thoroughly skilled in managing respiratory depression in the event it should occur. Management of respiratory depression should commence with standard airway support. Pharmacologic reversal of the sedative agents is indicated but requires an adequate training.
- Airway obstruction must be distinguished from respiratory depression. Although obstruction may result in hypoventilation, the patient's actual drive to ventilate (breathe) may or may not be

obtunded. Upper airway obstruction may be attributed to anatomical structures or foreign material, both of which are addressed during the initial “airway patency” portion of the primary assessment. When these procedures fail to establish patency, pathological causes of obstruction must be considered, namely laryngospasm or laryngeal oedema. These events can be distinguished visually by those trained in direct laryngoscopy, but otherwise the distinction is made empirically.

- Hypotension. Numerical values that change significantly from baseline should alert the clinician, but evaluation of skin colour changes and patient’s consciousness can guide the clinician to maintain an adequate value of blood perfusion. In general, a systolic pressure of 90 mm Hg should sustain mean arterial pressure sufficiently to perfuse tissues in the recumbent patient.
- Hypertension. “Hypertensive crisis” is the conventional term for sudden elevations in diastolic pressure ≥ 120 mmHg. A hypertensive crisis is regarded an “urgency” if the patient remains asymptomatic and an “emergency” if signs or symptoms are present, such as chest pain, headache, or visual disturbances.
- Chest pain: angina/myocardial infarction
- Cardiac arrest
- Allergic reactions. The spectrum of allergic reactions can include a minor local reaction to more severe anaphylactic reactions. The diagnosis of anaphylactic reaction is not always easy to establish. Anaphylactic reactions can present with mild dyspnoea in mild cases or lead to hypotension and shock in severe cases. When a life threatening anaphylactic reaction does occur, it simulates an acute cardiac, respiratory and metabolic crisis and requires urgent acute critical care. Treatment for anaphylactic reactions includes the discontinuation of the suspected allergen, airway management, fluid resuscitation, anti-histamine drugs, hydrocortisone and epinephrine.

Minor problems as:

- Vasovagal reactions
- Arrhythmia
- Pain and stress in patients

- Hallucinations
- Nausea and vomiting are common side effects of opioids. Additionally, the over distension of the stomach or colonic loop can produce nausea and vomiting after the endoscopic procedure.
- Hypersalivation

GAPS IN EVIDENCE AND FUTURE RESEARCH

There are still grey areas not supported by strong evidence from the literature based on randomized controlled trials and prospective studies. For some topics as monitoring, the lack of evidence is balanced by common sense as the advent of advanced monitoring as peripheral oxygen saturation has dramatically increase the safety during the administration of sedative and analgesic drugs detecting episodes of hypoventilation that could lead to life-threatening events. There are other areas as the use of processed EEGs that could lead in the future to the use of automatic closed-loop systems that could help the clinician titrating the dosage of sedative and analgesic drugs to a level of consciousness where the patient is still in a safe zone that allow him/her to preserve a normal ventilation and hemodynamic stability.

The real gap in the evidence is represented by the training competences required to consider the clinician competent in providing safely PSA. This represents the real challenge in the future of this practice as there is the need for at least prospective trials comparing the outcome of patients undergoing PSA when this is administered by an anaesthesiologist or by a non-anaesthesiologist. At the moment, PSA is still associated with predictable and non-predictable adverse events and complications and the role of the clinician involved in the management of PSA is to have the skills to manage the whole process and it's side effects. Quality control studies are necessary to evaluate the incidence of complications, their risk factors and the way to avoid them. Moreover, they could provide data to allow each centre to evaluate its performance (benchmarking).

SUMMARY

Procedural sedation and analgesia is a common practice in hospital and office-based services. In the near future, there will be an increasing number of requests for procedures requiring PSA. An adequate

pre-evaluation of the patient is mandatory to establish a risk factor for possible complications related to the administration of drugs that alter the level of consciousness and can lead to major and minor adverse events. The health provider involved in this process needs a specific training and advanced skills in managing airways and administering emergency drugs in case this would be necessary. There is still a debating question whether the management of PSA has to be centralized in the anaesthesia department. The role of anaesthesiologists should be maintained to coordinate and supervise PSA activities to keep the highest level of safety.

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Table 1- The 15 GRADE factors

Section A. factor 1 Outcome factor	Critical	Important	Less important	Not important
Section B. Factors 2-10 The 9 GRADE quality factors	study design Quality starting factor	Quality of evidence	The 5 downgraders Quality is lowered if ^s	The 3 Upgraders Quality is raised if ^s
	Randomized trials →	High	Limitations of design -1 Serious <input type="checkbox"/> -2 Very serious <input type="checkbox"/>	Large effect + 1 Large <input type="checkbox"/> + 2 Very large <input type="checkbox"/>
		Moderate	Inconsistency -1 Serious <input type="checkbox"/> -2 Very serious <input type="checkbox"/>	Dose response + 1 Evidence of a gradient <input type="checkbox"/>
	Observational studies →	Low*	Indirectness -1 Serious <input type="checkbox"/> -2 Very serious <input type="checkbox"/>	Antagonistic bias + 1 All plausible confounding would reduce the effect, or + 1 Would suggest a spurious effect when results show no effect <input type="checkbox"/>
		Very low*	Imprecision -1 Serious <input type="checkbox"/> -2 Very serious <input type="checkbox"/>	
	Total Points → <input type="checkbox"/>		Publication bias -1 Likely <input type="checkbox"/> -2 Very likely <input type="checkbox"/>	
Section C. Factors 11-15[®] The 5 GRADE transformers	Overall judgment on outcome(s)	Critical	Important	Less important
	Overall quality of evidence across outcomes	High	moderate	Low (& very low)
	Benefit/cost ratio	favorable	uncertain	unfavorable
	Benefit / harm ratio	favorable	uncertain	unfavorable
	Certainty about similarity in values/preferences	Highly similar	uncertain	widely variable

\$ = move up or down one point-grade (for example from high to intermediate)

* = move up or down two points-grades (for example from high to low)

RCT= 4 points

Observational studies = 2 points

Low and very low levels can be combined in one level

Table 2: Levels of quality of evidence

Level*	#Points	Quality	Interpretation
A	≥ 4	High	Further research is very unlikely to change our confidence in the estimate of effect or accuracy.
B	= 3	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect or accuracy and may change the estimate.
C	≤ 2	Low*	Further research is very likely to have an important impact on our confidence in the estimate of effect or accuracy and is likely to change the estimate.OR Any estimate of effect or accuracy is very uncertain(very low)

*Level C = can be divided into low (points =2) and very low (points=1 or less)

Points are calculated based on the 9 GRADE quality factors (Table 1 section B)

Table 3: E-to-R table (Evidence-to-Recommendation table)

Draft Recommendation

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Does the draft recommendation above address strategy that has more than one outcome YES NO[†]

The 5 Transforming Factors	Decision	Explanation
<p>1. Multiple Outcomes Importance Outcome 1 _____ its rank _____ Outcome 2 _____ its rank _____ Outcome 3 _____ its rank _____ The more important the outcome, the more likely is a strong recommendation</p>	<p>The most important outcome is _____</p>	<p>Rank: 9 =extremely important (critical) 1=extremely unimportant with 3 regions 7-9 important, 4-6 less important and 1-3 unimportant Your notes:</p>
<p>2. Quality of evidence* Outcome 1 _____ its evidence quality _____ Outcome 2 _____ its evidence quality _____ Outcome 3 _____ its evidence quality _____ The higher the quality of evidence, the more likely is a strong recommendation[§]</p>	<p>The overall quality across outcomes <input type="checkbox"/> High <input type="checkbox"/> moderate <input type="checkbox"/> low</p>	<p>If multiple outcomes, overall quality will follow that of the most important outcome (e.g. of the critical). If multiple equal outcomes (e.g. all have equal importance), then follow the least quality Your notes:</p>
<p>3. Benefit /Harm ratio The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/weak recommendation.</p>	<p><input type="checkbox"/> 9 <input type="checkbox"/> 8 <input type="checkbox"/> 7 <input type="checkbox"/> 6 <input type="checkbox"/> 5 <input type="checkbox"/> 4 <input type="checkbox"/> 3 <input type="checkbox"/> 2 <input type="checkbox"/> 1</p>	<p>9 =extremely favorable 1=extremely unfavorable with 3 regions 7-9 favorable, 4-6 uncertain and 1-3 unfavorable Your notes:</p>
<p>4. Benefit/Cost ratio The higher the costs of an intervention and other cost related to the decision – that is, the more resources consumed – the more likely is a conditional/weak recommendation. Are the resources consumed worth the expected benefit?</p>	<p><input type="checkbox"/> 9 <input type="checkbox"/> 8 <input type="checkbox"/> 7 <input type="checkbox"/> 6 <input type="checkbox"/> 5 <input type="checkbox"/> 4 <input type="checkbox"/> 3 <input type="checkbox"/> 2 <input type="checkbox"/> 1</p>	<p>9 =extremely favorable 1=extremely unfavorable with 3 regions 7-9 favorable, 4-6 uncertain and 1-3 unfavorable, Your notes:</p>
<p>5. Degree of certainty about similarity in values/preferences The smaller the variability or the greater the certainty around values and preferences, the more likely is a strong recommendation</p>	<p><input type="checkbox"/> 9 <input type="checkbox"/> 8 <input type="checkbox"/> 7 <input type="checkbox"/> 6 <input type="checkbox"/> 5 <input type="checkbox"/> 4 <input type="checkbox"/> 3 <input type="checkbox"/> 2 <input type="checkbox"/> 1</p>	<p>9 =extremely certain of similarity 1=extremely certain of variability with 3 regions 7-9 expected similarity, 4-6 uncertain and 1-3 expected wide variability in values and preferences Your notes:</p>

[†] If No (i.e., one outcome) then please list in factor 1&2 the previously determined initial ranking of outcome and quality level guided by the Initial quality of evidence that is presented to the panel in the Summary Of Findings (SOF) tables (ideally should be determined by independent methodologist). [§]Some exceptions may apply

After assessment of the above 5 factors, Please rank your approval (appropriateness) of the above draft recommendation.

Keeping in mind that 9 =totally approve (extremely appropriate) 1= totally disapprove (extremely inappropriate) **With 3 regions:**
 Approval (Appropriate) region: 7-9; Uncertain region: 4-6; Disapproval (Inappropriate) region: 1-3.

My vote for the above draft recommendation is:
 9 8 7 6 5 4 3 2 1