NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Intravenous Midazolam Administration for Conscious Sedation

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

Version Number:	3
Does this version include changes to clinical advice:	No
Date Approved:	23rd November 2018
Date of Next Review:	23rd November 2021
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Approval Group:	Medicines Utilisation Subcommittee of ADTC

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Approved by:	Medicines Utilisation Subcommittee of ADTC

Guideline Summary

Background: These guidelines were written in response to a Rapid Response Report from the NPSA in 2009 regarding the safe use of midazolam following a number of incidents with this drug.

Staff: Staff should be suitably trained in the administration of sedation including the required monitoring and resuscitation of the patient. They should only use sedative drugs that they are familiar with. It is recognised that they should be trained in at least Basic Life Support and higher levels of training are desirable. It is also recognised that administration of procedural sedation requires two trained personnel as a minimum.

Patient Selection: Patients should be assessed prior to receiving sedation with respect to comorbidities and concurrent medication to allow an informed decision about the safety of sedation. High risk cases may require the assistance of an anaesthetist. Appropriate fasting should be observed prior to elective cases. It is recognised that patients with an American Society of Anaesthetists (ASA) grading of three or greater should only be sedated in a hospital with immediate access to a cardiac arrest team/ anaesthetic support.

Equipment: Areas where sedation is administered should have the following equipment immediately to hand: a sufficient supply of oxygen, suction, facilities to hand ventilate the patient, emergency drugs including appropriate reversal agents, a defibrillator and appropriate airway adjuncts. Beds and trolleys must be capable of being tipped head down.

Monitoring: Appropriate monitoring facilities should be available when midazolam is administered. Pulse oximetry should always be used with Non Invasive Blood Pressure (NIBP) and ECG monitoring immediately available in hospital areas. These should be used as standard in high risk patients (ASA 3 and above). In areas only dealing with low risk patients (ASA 1 or 2) ECG monitoring may not be necessary. If capnography is available and suitable to the procedure, this should also be used. In any area, there should be a nominated member of staff to monitor and record the patient's physiological variables, including conscious level. If verbal contact is lost, then the patient needs a level of care equal to that of general anaesthesia and as such requires an anaesthetist to be called.

Drugs and Dosing: Staff should only use drugs with which they are familiar. A single agent will suffice in most cases. If an opioid is required for analgesia, it should be administered first before a lower dose of midazolam is given. Oxygen should always be available and will usually be indicated, but may not always be necessary and in some case may be detrimental e.g. patients with chronic respiratory disease and hypercapnia. Midazolam doses should reflect age, weight and comorbidities as per the manufacturer's recommendations. Reversal agents should **not** be used to hasten recovery to allow earlier discharge but should be available for emergency use. If a reversal agent is required, the patient should be monitored for at least 4 hours post reversal dose and a datix form should be completed for audit purposes. Agents such as propofol and ketamine should not be used for conscious sedation by anyone who has not had sufficient anaesthetic training and experience.

Recovery and discharge: Patient monitoring and oxygen therapy should continue during recovery with adequate staff present and resuscitation equipment available. If patients need airway support, are suffering from cardiovascular instability or are unable to communicate, they will need a one-to-one nursing ratio. Discharge criteria relating to their clinical condition and home circumstances should be met prior to discharge.

Background

Midazolam is a sedative agent commonly used to alleviate anxiety and ensure patient comfort and cooperation during potentially uncomfortable procedures such as endoscopy and colonoscopy. The vast majority of time, midazolam is used safely and effectively, however, a National Patient Safety Agency (NPSA) Rapid Response Report in 2008 highlighted that 498 incidents had been reported to them over a four year period where an inappropriate dose had been administered to a patient[1]. Three deaths had occurred as a result of these errors. This echoed a National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2004 which suggested that 14% of the 1818 deaths related to GI endoscopy that had been reported to it had received inappropriate sedation[2]. Both these publications recommend that local guidelines should be developed to aid the safe use of sedation and of midazolam in particular.

These guidelines refer to the use of midazolam for *Conscious Sedation* which is defined as "a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which **verbal contact with the patient is maintained throughout the period of sedation.** The drugs and techniques used to provide conscious sedation should carry a margin of safety, wide enough to render loss of consciousness unlikely". It is important to note that the end point is to maintain verbal contact with the patient. If this is lost, then the patient requires a level of care identical to that needed for general anaesthesia[3]. The use of alternative endpoints such as gag or eyelash reflexes is dangerous as these are signs of general anaesthesia, not sedation, and only serve to confuse the issue.

These guidelines have been developed by summarising the content of several national documents from a variety of specialties. Although there are many areas of agreement, there may be small differences in management between individual procedures and specialties. As such the reader is advised to use this document in combination with any relevant national guidance particular to their individual specialty or procedure. Examples of such guidance can be found in the references.

These guidelines are not applicable for the use of midazolam for control of symptoms in palliative care patients – alternative guidelines are available for care of these patients.

There are six main areas where recommendations are made: staff, patient selection, equipment, monitoring, drugs and dosing, and recovery and discharge

Staff

Staff involved in the administration or monitoring of patients receiving sedation should be knowledgeable of the pharmacology of the drugs that are administered, the dose, predicted onset time and time to peak effect of the drugs they administer and the potential for synergism between agents[1-5]. They should only use drugs with which they are familiar with. They should also be

appropriately trained in resuscitation[4,5]. In specialties with regular exposure to sedation, trainees should have sedation training monitored as part of their ongoing Annual Review of Competence Progression (ARCP). Career grade staff should be able to demonstrate continued experience in the practice of sedation and appropriate ongoing CPD[3,4].

As a bare minimum, there must be two members of staff present whenever midazolam is administered. One of these must be at least Basic Life Support (BLS) certified[3,4,5,6], with Immediate or Advanced Life Support certification being highly desirable.

This level of staffing is the minimum required for low risk procedures and patients. Higher levels of training/ staff numbers/ skill mix will be required if the patients receiving sedation are either acutely unwell (e.g. endoscopy for GI bleeding), suffer from chronic poor health (e.g. ASA 3 or above) or are undergoing higher complexity procedures. In these cases anaesthetic support should be requested before starting the procedure.

Patient Selection

Patients should be assessed prior to commencing sedation with regard to the following factors:

- Chronic health status especially cardiorespiratory disease,
- Age and body habitus,
- Relevant concurrent medication (such as opioids or other sedative agents).

These factors should be taken into account before deciding whether sedation will be safe in regard to the sedationist's experience, training and surroundings (e.g. community or hospital location), required monitoring, the initial dose of sedative agent (see recommendations on dosage). Patients should be graded according to the American Society of Anaesthesiologist (ASA) physical status classification system (see Appendix 1).

Specifically, the following conditions should alert the practitioner to a potentially hazardous procedure (see appendix 1 for scoring systems):

- Severe respiratory disease (MRC dyspnoea score 4 or more),
- Morbid obesity (BMI>35),
- Sleep Apnoea Syndrome,
- Severe cardiac disease (NYHA score 3 or more) or unstable angina
- Myasthenia Gravis
- Chronic Kidney Disease (CKD stage 4/5)
- Impaired hepatic function
- History of alcohol/ drug abuse
- Concomitant use of other CNS depressants including alcohol

Such patients may on occasion require the assistance of an appropriately trained anaesthetist and consideration should be given to this prior to embarking on the procedure.
Patients should also have a drug history assessed for potential interactions with their usual medication and to assess allergy status. There are a number of drugs which can affect the half-life and plasma concentration of midazolam. Certain antifungals, antibiotics, anticonvulsants, antivirals, antiemetics, calcium channel blockers, statins and herbal medicines have all been implicated in altering the pharmacokinetics of midazolam though this list is not exhaustive. The British National Formulary (BNF) and the manufacturer's data sheet should therefore be consulted for an up to date list of potential interactions.

Please note: In an overdose situation, an increase in the terminal half-life of midazolam (due to an interacting drug) may alter the efficacy of flumazenil and necessitate extended monitoring.

In some circumstances, local anaesthetic techniques may obviate the need for sedation and this should always be considered prior to embarking on a sedative technique. If both local anaesthetic and sedation are used, caution should be exercised and a smaller sedative dose considered.

All elective patients should observe standard fasting guidelines as appropriate to the relevant specialties national guidance prior to sedation (see Appendix 2). If there are no guidelines for the practitioners specialty, fasting should be as per the Association of Anaesthetists of Great Britain and Ireland recommendations (no solid food, milk or carbonated drinks for six hours preoperatively and no clear fluids for two hours preoperatively). These guidelines should only be deviated from after the relative risks and benefits have been considered – e.g. endoscopy for ongoing haemorrhage.

ASA 3 or above patients should only be sedated in a hospital environment[4], which has immediate access to a cardiac arrest team or anaesthetic medical support, by an experienced practitioner.

Equipment

Sedation should only be administered in an environment with suitable resuscitation facilities including:

- a sufficient supply of oxygen, suction
- facilities to hand ventilate patients (e.g. self-inflating bag and suitable face masks),
- emergency drugs including:
  - flumazenil (*Anexate*®)
  - naloxone (*Narcan*®) if opioids are to be used,
  - resuscitation drugs (such as adrenaline and atropine)
- a defibrillator
- appropriate airway adjuncts relevant to the skills available such as oral and nasal airways, laryngeal mask airways, and endotracheal tubes and laryngoscopes if a relevantly trained practitioner is available
- beds and trolleys should only be used if they can be tipped head down [3,4,5].

In ward areas, it would be more suitable to use designated treatment rooms rather than the bedside to perform procedures to allow sufficient room for monitoring equipment and additional staff.

Monitoring

Midazolam should never be administered without adequate patient monitoring facilities. Pulse oximetry should be used in every patient receiving sedation, with automated non-invasive blood pressure (NIBP) monitoring and ECG monitoring immediately available in hospital environments. If capnography monitoring is available and appropriate to be used in the procedure, its use is advised[3]. ECG and blood pressure monitoring should be used as standard in high risk patients[3,4,5], and would be advisable as routine. An exception to this is areas where midazolam is administered to carefully selected ASA 1 and 2 patients only, such where only pulse oximetry and NIBP monitoring is considered necessary[7]. This monitoring should be continued during recovery until discharge criteria have been met. There should be a nominated member of staff to monitor and record the patient's conscious level, respiratory rate and measured variables[2,3,4,6].

Verbal contact should be possible throughout the procedure. If this is lost and the patient only responds to stimuli such as pain, eyelash reflex or the gag reflex, then this is now commensurate with a general anaesthetic and requires the presence of an anaesthetist[3,4,5].

The AVPU score is a useful guide in this regard, with a target of keeping patients conscious level either "A" or "V" *(appendix 1)*.

Full monitoring should be immediately available in every area where intravenous sedation is administered.

Drugs and dosing

Clinicians should only use drugs with which they are familiar and have been trained in the administration of[4,5]. In most cases, a single agent will be sufficient and is far safer than using a combined technique of a sedative agent with an opioid as these drugs often display synergistic effects[3,5]. If pain is an issue, then the opioid should be administered first and given time to take effect before a lower dose of a sedative agent is administered. Intravenous access must be secured throughout the procedure. Doses of drugs should be reduced in the elderly and those with significant co-morbidities.

Patients should have a drug history assessed for potential interactions with their usual medication and to assess allergy status. There are a number of drugs which can affect the half-life and plasma concentration of midazolam. Certain antifungals, antibiotics, anticonvulsants, antivirals, antiemetics, calcium channel blockers, statins and herbal medicines have all been implicated in

altering the pharmacokinetics of midazolam though this list is not exhaustive. The British National Formulary (BNF) and the manufacturer's data sheet should therefore be consulted for an up to date list of potential interactions.

Oxygen

All hospital patients receiving sedation should be assessed for the need for oxygen therapy. In the vast majority of cases the use of oxygen is safe and should be considered as a default position, but in some cases it may not be necessary or even detrimental to the patient (e.g. Chronic Respiratory Disease with raised CO2 on blood gases). Pulse oximetry should be used in all cases and oxygen therapy should be immediately to hand if not being used electively [3,4,5,6].

Midazolam (Intravenous)

Dosage should be determined on a mg/kg basis as detailed in the following table[8] and in the flowchart in appendix 4. Doses should be determined on *ideal* body weight, **unless this is higher than actual body weight in which case actual body weight should be used**. (To determine ideal body weight, please refer to the table in Appendix 3).

Dose	Healthy adults under 60 years old	Adults over 60 years old/ significant comorbidities
Initial dose	0.03 - 0.035 mg/kg	0.007-0.015mg/kg
Subsequent titration doses	0.015 mg/kg	0.007-0.015mg/kg

NOTE: Doses should be determined on *ideal* body weight **unless this is higher than actual body weight in which case actual body weight should be used**

A small starting dose as described in the table should be given (e.g. 0.5-1mg for a 70 kg adult over the age of 60) and further doses titrated up after allowing the initial dose to take effect. It should not be given at a rate faster than 1mg/ 30 secs and it should be remembered that midazolam takes 1-2 minutes to begin to work with its peak effect seen at 5-10 minutes[1]. The minimum effective dose should be given. A usual total dose range should be 2.5-5mg midazolam for young, healthy patients (with doses up to 7.5 mg being necessary on rare occasions) and of 1- 3.5mg in the elderly[8] or in those with significant comorbidities. Doses above this range are outwith the usual standard doses recommended in the BNF.

Only the 1mg/ml strength of midazolam injection should be used for conscious sedation. A 10mg/2 ml injection also exists for use in palliative care and practitioners should ensure they are using the correct strength for their purposes.

Midazolam overdose may be treated with flumazenil (*Anexate*®) with an initial bolus dose of 200 micrograms, with repeated doses of 100 micrograms at one minute intervals until a suitable response has occurred[9]. It should be noted, however, that flumazenil has an elimination half life of 40-80 minutes compared to midazolam's half life of 90-150 minutes which may result in the patient becoming re-sedated after the flumazenil has worn off. This is especially important in the elderly where the half life of midazolam can be prolonged fourfold, whereas flumazenil's remains unchanged[1].

As flumazenil can precipitate seizures, caution should be exercised in patients with the following[9]

- Epilepsy
- A medical condition known to lower the seizure threshold (e.g. intracranial space occupying lesion)
- Chronic use of a benzodiazepine

Flumazenil should never be used "routinely" to allow quicker recovery from a deeper level of sedation, or to hasten a patient's discharge home. If flumazenil is used, patients should be monitored for at least four hours to ensure the effects of midazolam have worn off.

The use of flumazenil when midazolam has been used for conscious sedation should be reported via the Datix reporting system for ongoing learning and audit purposes and any other local reporting systems.

Opioids

Morphine, pethidine and fentanyl have all been used to relieve painful aspects of procedures. All these drugs will increase the risk of respiratory depression with midazolam. It takes approximately 10 minutes for pethidine and 30 minutes for morphine to reach peak effect[10] and so unless a sufficient time is left before midazolam is administered, overdose can occur. Fentanyl is more rapidly acting with its peak effect being reached in approximately 2 minutes[10]. However, it is extremely potent and there is a significant risk of respiratory depression when used in conjunction with midazolam. All of these agents should only be used with midazolam in experienced hands in a well monitored and controlled environment.

Opioid overdose can be treated with naloxone (*Narcan*®*)*, 100-200 micrograms followed by a further 100 micrograms every 2 minutes[11]. In keeping with flumazenil, naloxone's duration of action (approximately 20mins) is significantly shorter than the corresponding duration of action for the opioids discussed above (approximately 30 minutes for fentanyl, and 240 minutes for morphine and pethidine[10])

If either flumazenil or naloxone is used to treat an overly sedated patient, the patient should remain in hospital for at least four hours after the administration to ensure the sedative or analgesic agent has worn off.

Other agents

Agents such as ketamine and propofol should not be used for conscious sedation by anyone without sufficient anaesthetic training and experience[3,5]. These drugs are anaesthetic agents with a narrow therapeutic index and their use is outwith the scope of these guidelines.

Monitoring and oxygen therapy (if required) should be continued during the recovery period[5]. There should be adequate staff to monitor patients during this time and access to resuscitation equipment.

If a patient needs airway support, is cardiovascularly unstable or is unable to communicate, they should be nursed on a one to one ratio[1,2].

It should be noted that a patient's conscious level may deepen once an uncomfortable stimulus is removed and respiratory depression may only be apparent during this time.

Patients should only be discharged once the following criteria have been met:

- Are conscious and orientated,
- Are cardiovascularly stable
- Are able to eat and drink
- Will be accompanied by a responsible adult who will remain with them for at least 12 hours
- Are given clear written instructions on whom to contact in case of complications
- Are advised not to drive, sign legal documents, operate machinery or consume alcohol for 24 hours following administration of sedative drugs[5,6].

References

1. National Patient Safety Agency. *"Reducing Risk of Overdose with Midazolam Injection in Adults"* NPSA/2008/RRR011. December 2008 Available from http://www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=59896
2. NCEPOD. *"Scoping our Practice"*2004. Available from www.ncepod.org.uk
3. Academy of Medical Royal Colleges "*Safe Sedation Practice for Healthcare Procedures: Standards and Guidance"*, www.aomrc.org.uk October 2013
4. Intercollegiate Advisory Committee for Sedation in Dentistry. *"Standards for Conscious Sedation in the Provision of Dental Care"* 2015
5. British Society of Gastroenterology Endoscopy Section Committee Working Party. *"Recommendations for Standards of Sedation and Patient Monitoring during Gastrointestinal Endoscopy"*. September 2003
6. Royal College of Radiologists. "*Safe Sedation, Analgesia and Anaesthesia within the Radiology Department"* 2003
7. Scottish Dental Clinical Effectiveness Programme. *"Conscious Sedation in Dentistry"* 2006
8. Roche Pharmaceuticals. Summary of product characteristics, *Hypnovel 10mg/2ml.* 5th March 2008.
9. Roche Pharmaceuticals. Summary of Product Characteristics, *Anexate 0.1mg/ml*. 15th June 2011
10. Sasada & Smith. *"Drugs in Anaesthesia and Intensive Care"*, 2nd Edition Oxford University Press 1997

11. Hameln Pharmaceuticals. Summary of Product Characteristics, *Naloxone 400mcg/ml*. 15th June 2008

Additional resources

RCOA. "Guidance on Provision of Anaesthetic Services, Chapter 19 Guidance on Provision of Sedation Services" 2016 www.rcoa.ac.uk/system/files/GPAS-2016-19-SEDATION.pdf
Du rand IA et al: "British Thoracic Society Guideline for Diagnostic Flexible Bronchoscopy in Adults"; *Thorax* 2013;**68**: i1-i44

Appendix 1: Scoring systems used in the guidelines

1. American Society of Anaesthesiologists Physical Status Classification System

Grade	Description	Example
1	A normal healthy patient	No comorbidities
2	A patient with mild systemic disease	Well controlled asthma; controlled hypertension
3	A patient with severe systemic disease	Poorly controlled asthma; frequent angina
4	A patient with life-threatening systemic disease	Unstable angina; respiratory disease requiring home oxygen/ severely limiting daily activities
5	A moribound patient who is not expected to survive 24 hours with or without the operation	Ruptured abdominal aortic aneurysm
6	A declared brain-dead patient whose organs are being removed for donor purposes	

2. AVPU scoring

Score	Description
A –Alert	A fully awake patient
V – Voice	The patient responds to a vocal stimuli
P- Pain	The patient only responds to a painful stimuli
U – Unresponsive	The patient does not respond to any stimuli

3. New York Heart Association Functional Classification

Grade	Description
I	No symptoms during normal activity (e.g. walking, climbing stairs)
II	Slight symptoms (shortness of breath and/or angina) and slight symptoms during normal activity
III	Marked limitation in activity due to symptoms even during less than ordinary activity (e.g. walking 20 – 100 yards). Comfortable only at rest
IV	Severe limitations, symptoms even at rest

4. Medical Research Council Dyspnoea Scale

Score	Description
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after about 100m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

Appendix 2: Fasting Guidelines

Specialty	Clear fluid, water, black tea or coffee	Solids (including milky drinks)
Dentistry	Fasting not usually required	Fasting not usually required
Upper GI Endoscopy	2 hours pre-procedure	4 hours pre-procedure
Radiology	2 hours pre-procedure	6 hours pre-procedure
Anaesthetics	2 hours pre- procedure	6 hours pre-procedure

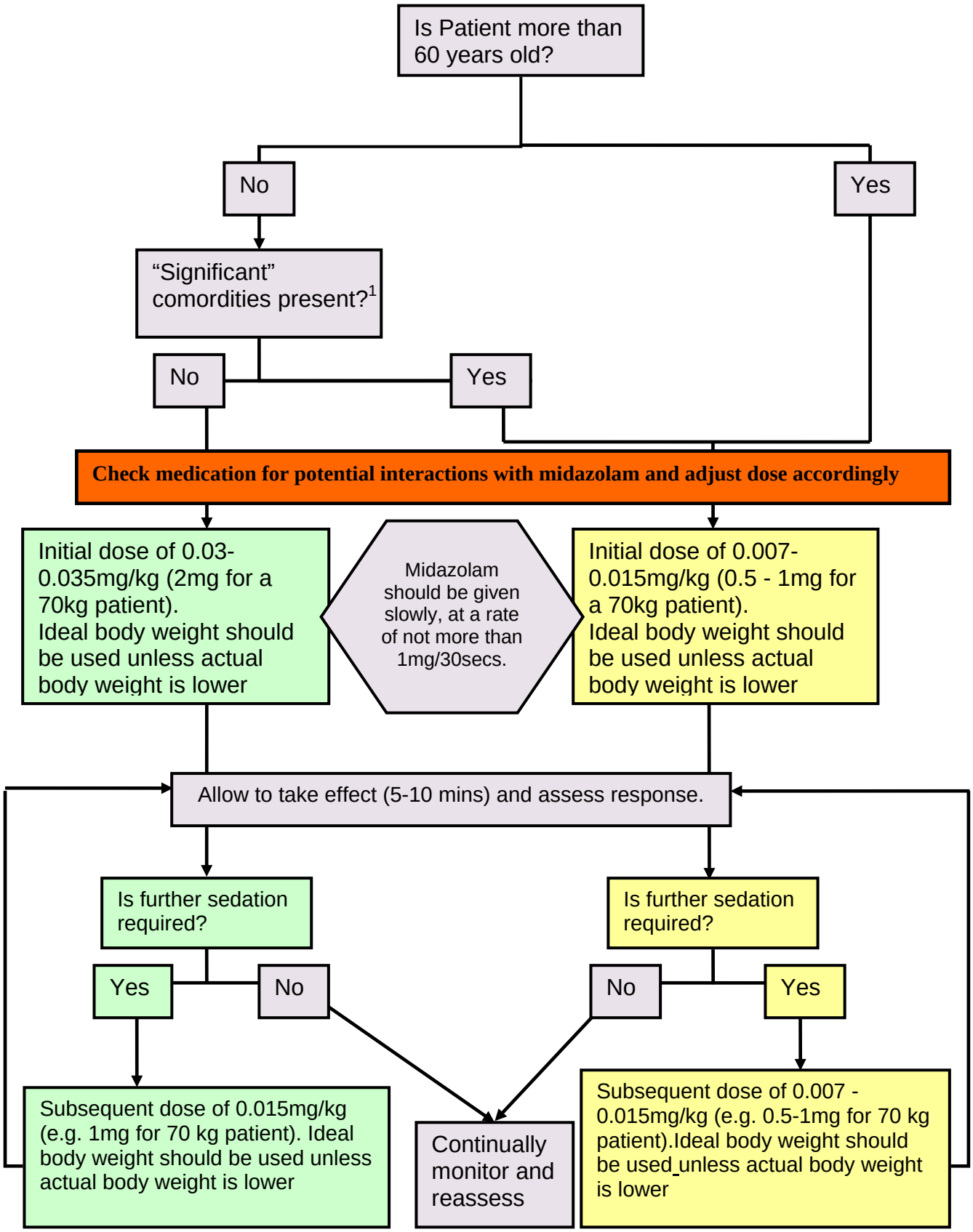
Please note:
In radiology and anaesthetics, chewing gum is allowable up to 2 hours pre-procedure as long as it is not swallowed.

Appendix 3: Ideal Body Weight (IBW) Estimation

IF IBW IS HIGHER THAN ACTUAL BODY WEIGHT, ACTUAL BODY WEIGHT SHOULD BE USED

Height Feet/inches	Height cm	Female IBW kg	Male IBW kg
5’	152	45.5	50
5’1”	155	47.8	52.3
5’2”	157	50.1	54.6
5’3”	160	52.4	56.9
5’4”	163	54.7	59.2
5’5”	165	57	61.5
5’6”	168	59.3	63.8
5’7”	170	61.6	66.1
5’8”	173	63.9	68.4
5’9”	175	66.2	70.7
5’10”	178	68.5	73
5’11”	180	70.8	75.3
6’	183	73.1	77.6
6’1”	185	75.4	79.9
6’2”	188	77.7	82.2
6’3”	190	80	84.5
6’4”	193	82.3	86.8

Appendix 4 : Recommended Midazolam Dosing Regime for Conscious Sedation



The manufacturers maximum recommended dose is 7.5mg in any single procedure for patients under the age of 60 or 3.5mg in those over 60 or with significant comorbidities. Doses should be titrated up and maximum doses should be rarely required

[1]*e.g. cardiorespiratory disease interfering with daily activities, severe hepatic or severe renal failure*