Table 1: Summary of the selection criteria.

Exclusion criteria:

a. Timing (Jan 2000 and March 2016)
b. None of the following uses: procedural sedation for surgical procedures, as part of burn care, ICU* sedation, uses for weaning patients off the ventilator, and emergency sedations that occur outside the context of "planned end-of-life care"
c. Language (documents developed in languages that were not the primary language of at least one of the investigators)

Inclusion criteria:

a. Document about palliative sedation, i.e. the deliberate lowering of a patient's level of consciousness using specified drugs within the last stages of life [49].
b. Document guides caregivers in approaching a problem.
c. Document describes some required care criteria.
d. Document provides some recommendations.
e. Document has a national (for countries) or regional coverage.
f. Document written in English or in one or the native languages of at least one of the investigators (Italian, Dutch, English).

*ICU means Intensive care unit

Table 2: Flowchart of guideline selection for Developmental Quality Appraisal and Comparison of content.

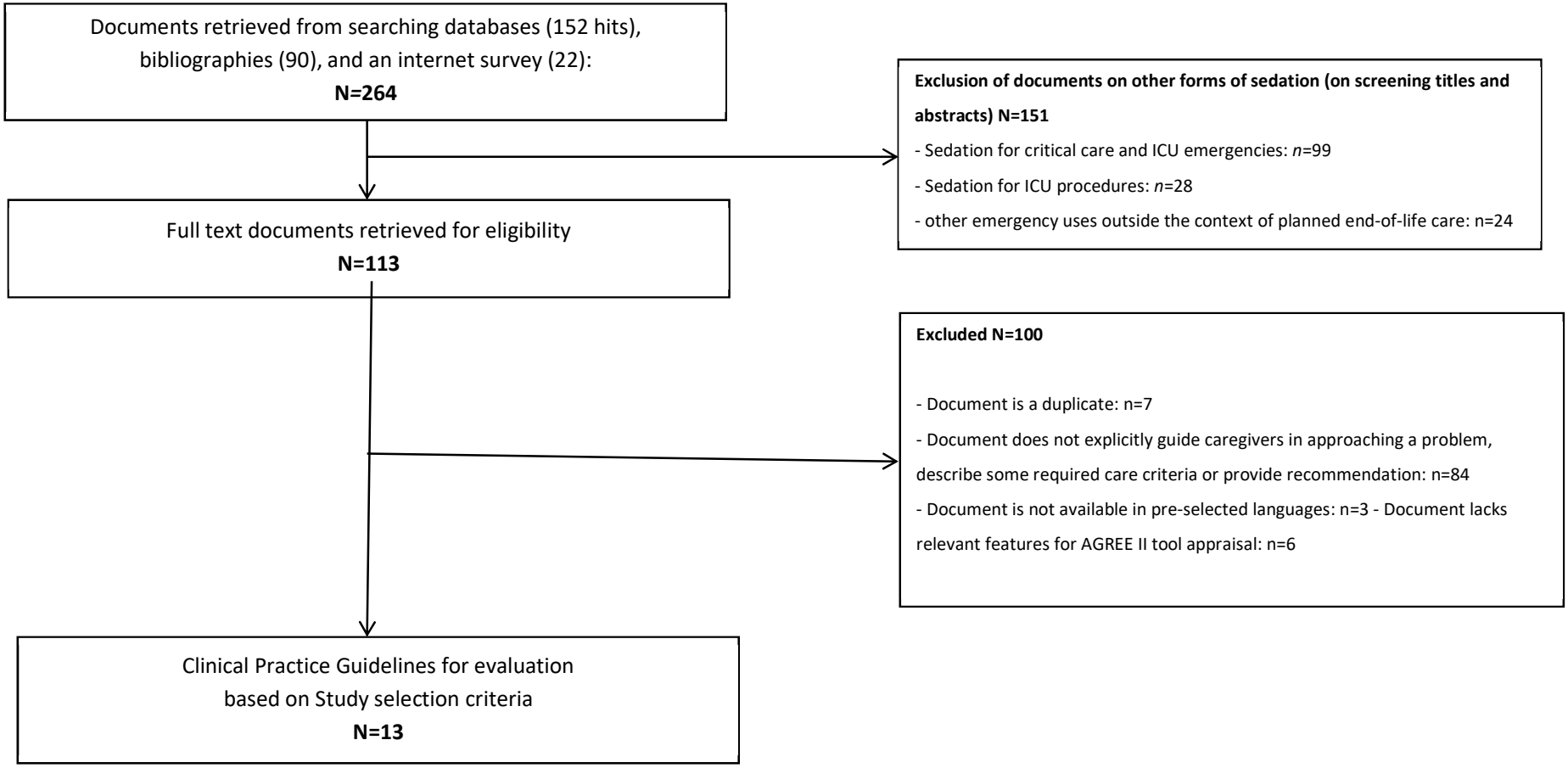

Table 3: Characteristics of the Clinical Practice Guideline

Country	Issuing body or organisation	Name/ title of guideline	Coverage	Length (in pages)	Year of development	If revised? (year): Planned next review? (year)	Professionals for whom it was developed	Patients for whom it was developed	Care-setting	Basis for recommendations*
1. Belgium	Flemish Federation of Palliative Care (FPZV)	Palliative Sedation guideline	Region-wide	18	2012	No: NP	Team	Dying patients with multiple features of the terminal phase	Non setting-specific	Consensus-based
2. Canada	Alberta Health Services, Calgary Zone	Clinical Practice Guideline for Palliative Sedation	Region-wide	6	2003	Yes (2005,2009): NP	Team	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Consensus-based
3. Canada	Fraser Health Hospice (private providers of palliative care)	Refractory Symptoms and Palliative Sedation Therapy guideline	Nation-wide	33	2011	No: NP	PC Team	Patients facing terminal illness who may or may not have physical symptoms	Hospice, PCU, Home	Consensus and legal considerations
4. Canada	Palliative care professionals in Ottawa and the Champlain Region	Champlain Region Palliative Sedation Therapy Clinical Practice guidelines and Protocols	Region-wide	16	2010	No: Yes (2013)	Team	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Consensus-based
5. Ireland	Irish Association	Palliative Sedation	Nation-	4	2011	No:	Team	Patients facing	Non	Consensus-based

	for Palliative Care (IAPC)	guidelines: Discussion paper	wide			NP		terminal illness who may or may not have physical symptoms	setting-specific	
6. Italy	Italian Association for Palliative Care (SICP)	Recommendation of the SICP on terminal/palliative sedation	Nation-wide	47	2007	No: NP	Team	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Consensus-based
7. Japan	Japanese National task force & the Society of Palliative Medicine	Clinical Guideline for Palliative Sedation Therapy Using the Delphi Method	Nation-wide	48	2005	No: NP	Team	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Consensus-based
8. Netherlands	Royal Dutch Medical Association (KNMG)	Guideline for Palliative Sedation Royall Dutch Medical Association (KNMG)	Nation-wide	78	2005	Yes (2009): NP	Team	Patients with cancer (47%), disorders of cardiovascular (17%), pulmonary (6%), nervous system (4%), and "others" (26%).	Non setting-specific	Evidence-/ Consensus-based
9. Norway	Norwegian Medical Association	Guidelines for palliative sedation at the end of life	Nation-wide	2	2008	Yes (2014): NP	Physicians	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Not declared

10. Europe	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation	Not explicitly stated	10	2014	No: NP	Team	Patients with advanced cancer who suffer from severe symptoms that are refractory to other forms of treatment.	Oncology setting	Evidence-/ Consensus-based
11. Spain	Ministry of Health & Consumer Affairs and the Spanish NHS	Clinical Practice Guideline for Palliative Sedation	Nation-wide	11	2008	No: NP	Team	Patients facing terminal illness who may or may not have physical symptoms.	Non setting-specific	Consensus-based
12. USA	Hospice & Palliative Care Federation of Hospice & PC Federation of Massachusetts	Palliative Sedation Protocol	Region-wide	14	2004	No: NP	Team	Patients facing terminal illness who may or may not have physical symptoms	Non setting-specific	Consensus-based
13. USA	American College of Critical Care Medicine.	Recommendations for end-of-life care in the intensive care unit	Nation-wide	10	2008	No: NP	Team	Patients facing terminal illness who may or may not have physical symptoms	ICU	Consensus-based

***** Method of developing the recommendations, as stated by authors**: -** either evidence-based or consensus-based, **FPZV**: Federatie Palliatieve Zorg Vlaanderen; **KNMG**: Koninklijke Nederlandse Maatschappij ter bevordering van de Geneeskunde; **Team**: Multidisciplinary team including physicians and nurses, **PCU**: Palliative Care Unit, **NP**: Not provided

Table 4: Terms, definitions, types of practices mentioned by issuing bodies in the guideline

Issuing body	Terms applied and their definitions (where provided)	Average life expectancy	Definition of refractory Symptom (suffering)	Common refractory symptoms listed	Types of sedation	Statement on the practice of palliative sedation
1. Flemish Federation of Palliative Care (FPZV)	**Palliative sedation (PS)** "Involves a purposeful and deliberate lowering of the level of consciousness of the patient, to a level where one or more refractory symptoms are sufficiently suppressed"	≤ 1 week (Few days in cases of continuous sedation)	Refractory symptoms are symptoms that cause severe suffering and that cannot be managed in a normal way, i.e. without depression of consciousness (sedation) or unacceptable side effects. They include only physical, but also psychological and existential symptoms.	Pain, terminal delirium (with hallucinations, delusions and / or anxiety), terminal severe breathlessness	Light or mild/ deep, intermittent/ continuous	Palliative sedation is nothing more or less than a special form of symptom control. It should be centred on the notion of adequacy and proportionality.
2. Alberta Health Services, Calgary Zone	**Palliative sedation therapy (PST)** "is the process of inducing and maintaining deep sleep, in the final hours to days of life, for the relief of severe suffering caused by one or more intractable symptoms when all appropriate alternative interventions have failed to bring adequate symptom relief"	Within days	A symptom is considered refractory if it cannot be adequately controlled despite aggressive therapy that does not compromise consciousness.	Agitated delirium, dyspnoea, pain, bleeding	Deep, continuous	Palliative sedation is an effective symptom control strategy. The authors left the option open for a non-palliative care specialist who had some expertise in symptom management to fulfil the criterion.
3. Fraser Health Hospice providers of Palliative Care	**Palliative sedation therapy (PST)** "is a therapy that aims to relieve intolerable suffering from refractory symptoms by intentionally lowering a patient's level of consciousness in the last days of life, by proportional and monitored use of non-	Hours to days	Refractory symptoms are those where "all possible treatments have failed, or it has been determined that there is no method within the time frame and risk: benefit ratio the patient can tolerate".	Delirium, dyspnoea, pain, nausea and vomiting	Mild, intermittent	This body views PST as an extraordinary intervention requiring expertise. When used appropriately, patient experiences symptom relief and death occurs through the natural course of the underlying disease,

	opioid drugs"					usually within hours to days.
4. Palliative care professionals in Ottawa and the Champlain Region	**Palliative sedation therapy (PST)** "is the intentional continuous induction of a reduced level of consciousness in order to relieve a refractory symptom or symptoms in a patient who is at the end of life (i.e. last days and weeks). Its intent is to relieve suffering and not to hasten death"	Within days	A refractory or intractable symptom is defined as a symptom for which there is no appropriate treatment available within the given time frame that the patient can tolerate or for which the risk-benefit ratio is not acceptable to the patient. A symptom is deemed intractable if all other measures usually used to control the symptom have failed.	Intractable dyspnoea, delirium, seizures, pain and other intractable symptoms. Existential/ spiritual suffering, psychological suffering (e.g. fear of the future, wish for PST to avoid future suffering)	Light or mild/ deep, intermittent/ continuous	PST constitutes an ethically acceptable therapeutic option when done according to appropriate guidelines in a very small select group of patients that meet the criteria for PST.
5. Irish Association for Palliative Care (IAPC)	**Palliative sedation** "is the process of calming, and PS is the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and healthcare providers"	Hours to days	Occasionally in the palliative care setting a symptom persists despite intensive efforts to control it. Such a symptom is known to as being "refractory" Such symptom is uncontrolled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness. There are significant implications if a symptom is designated as refractory, as this suggests that it will not be relieved by routine measures.	Agitated delirium, dyspnoea, pain and convulsions. Emergency situations i.e. massive haemorrhage, severe terminal dyspnoea overwhelming pain crisis and severe non-physical refractory symptoms of existential, spiritual, emotional or psychological distress - when the prognosis is estimated in terms of hours or days.	Light, or mild, temporary, respite/ deep, intermittent/ continuous	The IAPC considers sedation to be an important and necessary therapy in the care of selected palliative care patients with otherwise refractory distress.

6.	Italian Association for Palliative Care (SICP)	**Terminal sedation / Palliative sedation** "the intentional reduction of consciousness via supervised pharmacological means, until total loss of consciousness is achieved, in order to reduce (abolish) the perception of symptoms perceived as intolerable by a patient, despite the use of adequate and appropriate means of symptom control"	Hours to days	Symptoms are termed refractory when it remains otherwise intolerable and unresponsive, despite the use of adequate methods to control them.	Refractory dyspnoea, hyperactive delirium, pain, irrepressible vomiting, status epilepticus, total suffering, psychomotor restlessness, anxiety, psychological or existential distress.	Deep, continuous, Acute/ emergency	This guideline aims to increase awareness on various aspects of palliative sedation practice, by clarifying taxonomic aspects, homogenising practical applications (i.e. correct clinical and pharmacological aspects), increasing ethical awareness, and overall enhancing the management of communication and spirituality.
7.	Japanese National task force & the Society of Palliative Medicine	**Palliative sedation therapy** "is the use of sedative medications to relieve suffering by the reduction in patient consciousness level or intentional maintenance of reduction in patient consciousness level resulting from symptomatic treatments"	Days or weeks	Suffering is defined as refractory when all treatments have failed or when, on the basis of the patient's wishes and physical conditions, there are no other methods that will be effective within the allowed time frame and the possibility of complications and degree of invasion are tolerable for the patient.	Delirium (not associated with dementia), pain, dyspnoea; Excessive bronchial secretion, nausea and vomiting, fatigue, convulsion, myoclonus. Anxiety, depression and psycho-existential suffering (e.g. hopelessness, meaninglessness)	Mild, intermittent	This guideline stresses respect for individuality and humaneness, the necessity for symptom re-evaluation and the responsibility of primary clinicians.
8.	Royal Dutch Medical Association	**Palliative sedation** "the deliberate lowering of a patient's level of consciousness in the last stages of life"	1-2 weeks	A symptom is considered refractory if none of the conventional modes of treatment is effective or fast acting	Fatigue, pain, dyspnoea, confusion, nausea and vomiting, anxiety and	Mild/ deep, intermittent/ continuous	This guideline views palliative sedation as a normal medical procedure, which must therefore be

	(KNMG)			enough, and/or if these modes of treatment are accompanied by unacceptable side effects.	depression.		clearly distinguished from "termination of life".
9.	Norwegian Medical Association	**Palliative sedation** "pharmacological depression of the level of consciousness in order to alleviate suffering that cannot be relieved in any other way"	Few days	In situations where the patient cannot be helped unless his or her consciousness is reduced to a level at which communication with the patient is greatly reduced or has ceased.	Anxiety and distress, dyspnoea and pain	Mild/ deep, intermittent/ continuous	Palliative sedation should be an extraordinary measure initiated as a response to intolerable suffering that stems from, and is dominated by, physical symptoms. Mental suffering alone is not an indication for palliative sedation.
10.	European Society for Medical Oncology (ESMO)	**Palliative sedation** "is a measure of last resort used at the end of life to relieve severe and refractory symptoms. It is carried out by the administration of sedative medications in supervised settings and is aimed at inducing a state of decreased awareness or absent awareness (unconsciousness)".	At the end of life	Symptoms that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness.	Pain, dyspnoea, anxiety, and agitated delirium	Mild/ deep, intermittent/ continuous, emergency, respite	Sedation is a critically important therapeutic tool of last resort. Clear indications and guidelines for use are necessary to prevent abuse of this approach.
11.	Ministry of Health & Consumer Affairs and the Spanish NHS	**Palliative sedation** "is the deliberate administration of drugs, in the dosage and combinations required to reduce the consciousness of a patient with advanced or terminal illness, as much as	≤ 1 week	Suffering is understood as being refractory when all intervention possibilities run out, after one has determined the aspects of avoidable suffering that are possible via symptom	Pain, dyspnoea, delirium etc.	Mild/ deep, intermittent/ continuous	NP

	necessary to adequately alleviate one or more refractory symptoms, and with his or her explicit consent" **Sedation in agony** is a singular case of sedation via sufficiently deep and likely irreversible reduction of consciousness, in a patient whose death is foreseen to be very near.		control, psychosocial intervention, care of the environment etc.			
12. Hospice & Palliative Care Federation of Hospice & PC Federation of Massachusetts	**Palliative sedation (PS)** "is the monitored use of medications (sedatives, barbiturates, neuroleptics, hypnotics, benzodiazepines or anaesthetic medication) to relieve refractory and unendurable physical, spiritual, and/or psychosocial distress for patients with a terminal diagnosis, by inducing varied degrees of unconsciousness"	Hours to days	Refractory symptoms that justify the use of palliative sedation are symptoms that cannot be adequately controlled despite aggressive efforts by the interdisciplinary team to provide timely, tolerable therapies that do not compromise consciousness.	Not explicitly mentioned	Mild/ deep, intermittent/ continuous	PS in a setting other than a hospice inpatient unit or hospital requires the presence of continuous care licensed nurses for a minimum of the first twenty-four hours of care. A competent hospice team member must document daily confirmation of the effectiveness of the treatment.
13. American College of Critical Care Medicine	**Sedation within the context of end-of-life-care in the critical unit, Sedation in the critical care unit, Sedation during end-of-life care.**	Hours	NP	Dyspnoea, agitated delirium	Intermittent/ continuous	This guideline aims to improve the care of intensive care unit (ICU) patients during the dying process. End-of-life care is emerging as a comprehensive area of expertise in

	No explicit definition was provided					the ICU and demands the same high level of knowledge and competence as all other areas of ICU practice.

Table 5: Content of the Clinical Practice Guidelines: Life expectancy, symptoms, and the presence of core elements in the 10-item EAPC Framework

Issuing body	**10 Core recommendations enumerated in the EAPC Framework** x signifies the item was present; / signifies absent)										**Sum**[1]: Number of core recommendations of the EAPC framework that were present in the specific guidelines
	1-Recommend pre-emptive discussion of the potential role of sedation in EOLC	**2- Describe the indications in which sedation may be considered**	**3- Describe the necessary evaluation and consultation procedures**	**4- Specify consent requirements**	**5- Indicate the need to discuss the decision-making with the family**	**6- Present direction for selection of the sedation method**	**7- Present direction for dose titration, patient monitoring and care**	**8- Guidance for decisions regarding hydration and nutrition and concomitant medications**	**9- Care and informational needs of the patient family**	**10- Care for the medical professionals**	
1. Flemish Federation of Palliative Care (FPZV)	X	X	X	X	X	X	X	X	X	X	10/10
2. Alberta Health Services, Calgary Zone	/	X	X	X	/	/	X	/	/	/	4/10
3. Fraser Health Hospice providers of Palliative Care	X	X	X	X	X	X	X	X	X	X	10/10

4.	Palliative care professionals in Ottawa and the Champlain Region	x	x	x	x	x	x	x	x	x	/	9/10
5.	Irish Association for Palliative Care (IAPC)	x	x	x	x	x	x	x	x	x	/	9/10
6.	Italian Association for Palliative Care (SICP)	x	x	x	x	x	x	x	/	x	x	9/10
7.	Japanese National task force & the Society of Palliative Medicine	/	x	x	x	x	x	x	x	x	x	9/10
8.	Royal Dutch Medical Association (KNMG)	x	x	x	x	x	x	x	x	x	x	10/10

9. Norwegian Medical Association	/	x	x	x	x	x	x	x	x	/	8/10
10. European Society for Medical Oncology (ESMO)	x	x	x	x	x	x	x	x	x	x	10/10
11. Ministry of Health & Consumer Affairs and the Spanish NHS	x	x	x	x	x	x	x	/	x	/	8/10
12. Hospice & Palliative Care Federation of Hospice & PC Federation of Massachusetts	/	x	x	x	x	/	x	x	x	x	8/10
13. American College of Critical Care Medicine	x	x	/	x	x	x	x	/	x	x	8/10

Number of guidelines in which the specific recommendation was present	9/13	13/13	12/13	13/13	12/13	11/13	13/13	9/13	12/13	8/13	112/130

Key: x means present, / means absent

Table 6: Scaled domain scores[1] (%)/quality assessment of selected Clinical Practice Guideline using the AGREE II instrument (number of appraisers=5)

Issuing society	Scope & Purpose (Items 1-3) %	Stakeholder Involvement (Items 4-6) %	Rigour of development (Items 7-14) %	Clarity and presentation (Items 15-17) %	Applicability (Items 18-21) %	Editorial independence (Items 22-23) %	Overall Score[2] (on a scale of 1-7)	Would you recommend the use of this guideline[3]? Yes/Modify/No
1. Flemish Federation of Palliative Care (FPZV)	61	61	17	72	33	33	4	Modify
2. Alberta Health Services, Calgary zone	61	0	13	44	0	50	3	Modify
3. Fraser Health Hospice providers of Palliative Care	100	33	48	83	46	50	5	Modify
4. Palliative care professionals in Ottawa and the Champlain Region	100	56	25	67	29	50	5	Modify
5. Irish Association for Palliative Care (IAPC)	89	44	46	50	0	50	4	Modify
6. Italian Association for Palliative Care (SICP)	100	67	21	50	0	50	4	Modify
7. Japanese National task force & the	100	100	67	39	0	50	5	Yes

	Society of Palliative Medicine								
8.	Royal Dutch Medical Association (KNMG)	100	61	71	89	42	25	7	Yes
9.	Norwegian Medical Association	83	29	42	56	17	25	4	Modify
10.	European Society for Medical Oncology (ESMO)	83	67	46	89	54	33	5	Modify
11.	Ministry of Health & Consumer Affairs and the Spanish NHS	100	100	60	89	21	100	6	Yes
12.	Hospice & Palliative Care Federation of Hospice & PC Federation of Massachusetts	72	44	21	28	42	50	4	Modify
13.	American College of Critical Care Medicine	61	50	46	22	4	50	3	Modify

[1]Scale domain score = [Obtained score - Minimum possible score] x 100
[Maximum possible score - Minimum possible score]

[2] Overall score: on a scale of 1-7, where 1 = lowest and 7 =highest

[3] Recommendation: Yes/Modify/No: Key – we recommended a guideline for modification if its content was appropriate but 'rigour of development' domain score was ≤50%