Cancer Care Ontario
Action Cancer Ontario

Cancer Care Ontario's Symptom Management Guide-to-Practice: Delirium

Preamble

Ontario Cancer Symptom Management Collaborative

An initiative of Cancer Care Ontario, the Ontario Cancer Symptom Management Collaborative (OCSMC) was undertaken as a joint initiative of the Palliative Care, Psychosocial Oncology and Nursing Oncology Programs. The overall goal of the OCSMC is to promote a model of care enabling earlier identification, communication and documentation of symptoms, optimal symptom management and coordinated palliative care.

The OCSMC employs common assessment and care management tools, including the Edmonton Symptom Assessment System (ESAS) screening tool to allow patients to routinely report on any symptoms they are experiencing. Symptom Management Guides-to-Practice were developed to assist health care professionals in the assessment and appropriate management of a patient's cancer-related symptoms. In addition to the symptom specific Guides-to-Practice, quick-reference Pocket Guides and Algorithms were created. Additionally, for a comprehensive management plan for patients with advanced disease, please refer to the Palliative Care Collaborative Care Plans.

Objective

The objective of this initiative was to produce Guides-to-Practice for the management of patients with cancer-related symptoms. These documents are clinical tools designed to assist health care practitioners in providing appropriate patient care and are not intended to serve as standards of care.

Target Population

The target population consists of adult patients who require symptom management related to cancer. It is outside the scope of these Guides-to-Practice to address in detail the management of patients experiencing acute adverse effects secondary to systemic or radiation therapy. Please visit the Program in Evidence-Based Care for guidelines related to these topics.

Target Users

The Guides-to-Practice will be of interest to health professionals who provide care to patients with cancer-related symptom management needs at various stages of the disease pathway.

Methodology

The Guides-to-Practice were developed by the interdisciplinary Symptom Management Group (SMG) which included regional representation from across the province (refer to Post-amble for details). As an alternative to de novo development, the Guides-to-Practice were developed using the ADAPTE guideline adaptation approach that includes identifying existing guidelines, appraising their quality, selecting recommendations for inclusion and obtaining expert feedback (refer to Appendix A and B for details).

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Considerations

The following guidelines were used as the basis for the development of this Guide: the Fraser Health Hospice Palliative Care Program Symptom Guidelines on Delirium and Restlessness (1), Common Questions by Capital Health (2), and the National Comprehensive Cancer Network's (NCCN's) Palliative Care Practice Guidelines: PAL-18 (3).

Key recommendations are highlighted in shaded boxes. Source documents for each recommendation are denoted according to the symbols shown in Table 1. For example, if a recommendation is based on the expert opinion of the delirium working group, this is indicated by a check box, or if derived verbatim from the NCCN guideline, it is indicated by the symbol NCCN. Recommendations that are derived from the NCCN guideline but have been modified are designated as NCCN *Modified*.

Table 1. Sources of Evidence

Symbol	Definition
☑	Recommended best practice based on the clinical experience of the guide development group.
Fraser Health **Capital Health** **NCCN**	Sections extracted verbatim from guidelines.
Fraser Health ***Modified*** **Capital Health** ***Modified*** **NCCN** ***Modified***	Sections extracted from guidelines and modified to better reflect the Ontario context.

This Guide-to-Practice should be used in addition to the appropriate assessment and management of reversible, underlying causes of delirium. While some references to specific articles are provided, this Guide-to-Practice is not intended to be a comprehensive overview of delirium management; for a more in-depth review the reader is encouraged to seek out the original guidelines. For a quick reference tool on delirium, please refer to the Delirium Pocket Guide and Algorithm. A discussion regarding the moral and ethical issues related to palliative sedation is outside of the scope of this Guide-to-Practice.

Definition of Terms

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Delirium has been defined as a transient organic brain syndrome characterized by the acute onset of disordered attention and cognition, accompanied by disturbances of cognition, psychomotor behaviour and perception (2).

> ☑ **Delirium is considered a medical emergency in palliative care and should be treated/ managed immediately.**

Types of Delirium:

- Hypoactive – Hypoalert (4-7) often misdiagnosed as depression in the elderly
- Hyperactive – Hyperalert (5,8-12)

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- Mixed type – with fluctuations from hypoalert to hyperalert (6-9)

Restlessness can be defined as an inability to relax or be still, the quality of being ceaselessly moving or active or a feeling of agitation expressed in motion (5).

Terminal restlessness is best described as "agitated delirium in a dying patient, frequently associated with impaired consciousness" and non-purposeful movement (9).

Fraser Health *Modified*

> **It is important to keep in mind that confusion, altered mental state, cognitive impairment, acute brain syndrome, restlessness, dementia and delirium are often used interchangeably – although they have different meanings (5).**

Assessment

> ☑ **Delirium is a cognitive impairment with a sudden onset and fluctuating level of consciousness (4) therefore, ongoing comprehensive assessment is recommended.**

Fraser Health *Modified*

Ongoing comprehensive assessment is the foundation of effective management of delirium and restlessness including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. The OPRSTUV Acronym (Table 2) suggests some assessment questions; however these may need to be tailored to each patient. Where a patient is not able to complete an assessment by self-reporting, then the health professional and/or the caregiver may act as a surrogate.

Table 2: Delirium/Restlessness Assessment using Acronym O, P, Q, R, S, T, U and V (1)

Onset	When did it begin? Has it happened before?
Provoking / Palliating	Are there things which worsen the agitation? What makes it better? What makes it worse? How are you sleeping?
Quality	What does it feel like? Do you feel confused? Are you seeing or hearing anything unusual?
Region / Radiation	Do you know what day/month/year it is? Do you know where you are right now? Can you tell me your full name?
Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right Now? At Best? At Worst? On Average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom?
Treatment	What medications or treatments are you currently using? How effective are these? Do you have any side effects from the medications/treatments? What medications/treatments have you used in the past?
Understanding / Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?
*Physical Assessment (as appropriate for symptom), * Pertinent History (risk factors).	

Assessment must determine the cause, effectiveness of the treatment and impact on the quality of life for the patient and their family.

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The Mini-Mental State Examination (MMSE) (Appendix C) may be used as a screening tool to identify cognitive impairment. Further tools are required to assess and identify delirium such as: the Confusion Rating Scale (CRS) (Appendix D), Nursing Delirium Symptom Scale (NDSS) (Appendix E) and the Memorial Delirium Assessment Scale (MDAS) (Appendix F).

Diagnosis

Fraser Health ***Modified***

Management of delirium should include treating reversible causes where possible and desirable, according to the goals of care. Approximately 25 to 45 percent of episodes of delirium are reversible (2). The most significant intervention in the management of delirium/restlessness is treatment (medication and/or education) of the symptom itself and identifying and treating the underlying cause(s) as appropriate. Depending on the stage of disease, the treatment of an underlying cause may not be possible or indicated.

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Identifying the underlying etiology of delirium or restlessness is essential in determining the required interventions.

Fraser Health *Modified*

Watching for the "sun downing" effect (nocturnal confusion) is recommended as it may be the first symptom of early delirium (5,7,11,19).

Fraser Health *Modified*

Delirium is usually of multi-factorial etiology. Under-diagnosing is often a problem in delirium (4-6,11,12)**.** The decision to carry out investigations must be weighed against the value that will be gained from the results and the anticipated improvement from treatment.

In addition, the morbidity and 'usefulness' of pursuing investigations in a patient who may be deteriorating quickly and close to death (5,6,11), must be considered. The further along in the disease trajectory the less likely the delirium will be reversed (13).

A number of assessment tools exist to assist in the assessment of delirium (7,12) (Refer to appendices for details).

☑ **Orientation questions alone do not provide an accurate assessment of a person's cognitive function; therefore it is important to use a multipronged approach to perform a thorough assessment.**

The following are the DSM IV criteria for diagnosing delirium due to a general medical condition (1,6,14-16):

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- Disturbance of consciousness with reduced ability to focus, sustain and shift attention.
- Change in cognition (such as memory deficit, disorientation, language disturbances or perception disturbances not better explained by a pre-existing stabilized or evolving dementia).
- The disturbance develops over a short period of time and tends to fluctuate during the course of the day.
- There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

Causes of Delirium

The causes of delirium are usually multi-factorial (6-8,17).

☑ **It is recommended that determining the underlying etiology, educating/reassuring the patient/family and treating the symptoms occur simultaneously.**

Suggested Delirium Acronym

The acronym presented below may assist health care providers in quickly identifying or reviewing the multiple factors that could cause or contribute to delirium.

Capital Health *Modified*

Figure 1: Delirium Acronym - Adapted with permission from Capital Health (2)

D Drugs, drugs, drugs*, dehydration, depression
E Electrolyte, endocrine dysfunction (thyroid, adrenal), ETOH (alcohol) and/or drug use, abuse or withdrawal
L Liver failure
I Infection (urinary tract infection, pneumonia, sepsis)
R Respiratory problems (hypoxia), retention of urine or stool (constipation)
I Increased intracranial pressure
U Uremia (renal failure), under treated pain
M Metabolic disease, metastasis to brain, medication errors/omissions, malnutrition (thiamine, folate or B12 deficiency)

* Medications are a common cause of delirium.

Fraser Health *Modified*

Table 3 provides a summary of causes contributing to restlessness and agitated behavior of delirium; some of these causes are potentially reversible.

Table 3: Causes of Delirium - Adapted from Fraser Health Delirium/Restlessness (1)

Causes of Delirium (Potentially reversible)		Contributing factors
Neoplastic		Primary tumour of brain (8, 12, 15), metastases (1,8, 12, 15), tumour burden or location (5).
Infection/inflammatory		Pneumonia, urinary tract infection (1-5, 8, 9, 12, 14-16, 18, 20), cellulitis and other causes of sepsis.
Metabolic		Hypercalcemia, uremia, hypoglycemia, hyperglycemia, or hyponatremia (1, 5, 9, 12, 13, 15, 16, 18).
Drug Effects	*Idiosyncratic*	Anti-cholinergic drugs (6, 11, 13), anticonvulsants (18), antidepressants, antiemetics (8, 15), antihypertensives (8, 15), antiviral (8, 9, 15). Chemotherapy – vinca alkaloids, methotrexate, cisplatin, bleomycin, procarbazine (13,15,20), corticosteroids (1), H2 antagonists(1, 5, 8, 15, 20), neuroleptics (5) opioids (5, 12, 17).
	Overdosage	Due to physical deterioration (5), due to metabolic causes (1, 5), accidental (5, 15, 18), intentional – alcohol abuse (5, 20), prescription drugs, non-prescription drugs, recreational drugs.
	Drug withdrawal	Alcohol (18), barbiturates, benzodiazepines (5, 20), nicotine (5), opioids (1, 4, 8, 15), steroids (1, 8).
Cardiopulmonary		Cerebral hypoxia, hypercapnia, or cerebrovascular disease (5, 12).

Causes of Delirium (Potentially reversible)	Contributing factors
Dehydration	(8, 9, 21).
Endocrine dysfunction	Thyroid and adrenal (1, 8, 9, 15, 20).
Liver failure	Altered drug metabolism, hepatic encephalopathy (8, 13, 16, 20).
Malnutrition	Thiamine, folate or vitamin B12 deficiency (1-5, 8, 9, 15, 18).
Renal failure	Altered drug metabolism, excretion (1, 13, 15, 17, 21).
Trauma	Subdural hematoma, intra-cerebral hemorrhage (4, 5, 11, 14, 16, 19).
Causes of Restlessness	**Contributing Factors**
Physical	Pain /discomfort, constipation, urinary retention, hypoxia, metabolic, organ failure, fever, dehydration (1, 5, 8, 9, 21,22).
Drug Effect	Extrapyramidal effects, akathesia, opioid-induced neurotoxicity (5).
Psychosocial	Personal suffering, existential anguish, interpersonal conflict, spiritual angst/journey, worry, grief (5, 22).
Psychiatric	Delirium of any cause, dementia, anxiety disorder (4,7,14).
Imminently Dying	Any combination of the above with a state of consciousness that is altering, fluctuating and/or declining (5,14,16).
Visual or hearing impairment or linguistic barriers	(20).

Non-Pharmacological Treatment

Fraser Health *Modified*

It is important to provide explanation and to reassure the family that the symptoms of delirium will fluctuate, are caused by the illness, are not within the patient's control, and the patient is not going 'insane' (14,15).

It is important to understand that some hallucinations, nightmares, and misperceptions may reflect unresolved fears, anxiety or spiritual passage (25).

- Include the family in decision making, emphasizing the shared goals of care (15).
- Report hallucinations (18).
- Encourage the family to be present in a calming way (11,22).

Fraser Health *Modified*

- Instruct the family to provide gentle, repeated reassurance (5,12,15) and avoid arguing with the patient (5,11,15,16).
- Watch for the "sun downing" effect (nocturnal confusion), as it may be the first symptom of early delirium (5,7,11,19).
- Provide a calm, quiet environment and help the patient reorient to time, place and person (visible clock, calendar, well known or familiar objects) (6,7,15,19).
- Presence of a well known family member is preferred (6,7,15,22).

- Provide a well lit, quiet environment (5-7,11,12,14-16,22). Provide night light (4).
- To prevent over-stimulation, keep visitors to a minimum and minimize staff changes and room changes (12).

Fraser Health *Modified*

- Correct reversible factors – dehydration (7,17,21), nutrition (17), alteration in visual or auditory acuity (provide aids) (6,19), sleep deprivation (5,12).
- Avoid the use of physical restraints or other impediments to ambulation; avoid catheterization unless urinary retention is present (3).
- Encourage activity if patient is physically able (15).
- When mildly restless provide observation and relaxation techniques (massage, tub baths, gentle music) as applicable (15).

Pharmacological Treatment

☑ **It is important to recognize that delirium may interfere with optimal pain and symptom expression (self-reporting), assessment and management (13).**

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Reversible factors such as infection, constipation, pain, withdrawal, and drug toxicity should be corrected (9,16). However a firm diagnosis may only be attainable in less than half the cases (14).

Review medications; consider opioid rotation to reverse opioid neurotoxicity (4,8,11,14); discontinue unnecessary drugs; or prolong dosing interval for necessary drugs (5).

- If a patient is developing "sun downing" effect (confusion in the evening) (17), psychotropic drugs have a place in treatment.
- Anticipate the need to change treatment options if agitation develops – particularly in cases where patient, family and staff safety may become threatened (6,19).

Fraser Health *Modified*

- Benzodiazepines may paradoxically excite some patients (10,20) and should be avoided unless the source of delirium is alcohol or sedative drug withdrawal, or when severe agitation is not controlled by the neuroleptic (10) (Table 4).
- If patient has known or suspected brain metastases a trial of corticosteroids is worthwhile (7).
    - Dexamethasone 16 - 32 mg po daily in the morning (7) may be used however, this suggestion is made based on expert opinion and doses may vary from region to region.

☑ **Misinterpreting symptoms of agitation/restlessness, moaning and/or grimacing as poorly controlled pain, with subsequent administration of more opioids, can potentially aggravate the symptom and cause opioid neurotoxicity.**

Mild Delirium

☑ **Haloperidol is recommended as the gold standard for management of delirium (25).**

☑ **If titration with haloperidol is not effective consider using methotrimeprazine.**

NCCN *Modified*

- Evaluate primary therapy.
- Haloperidol 0.5-1 mg po / subcut bid-tid.
- Alternate agents:
  - Risperidone 0.5-1 mg po bid.
  - Olanzapine 2.5 – 15 mg po daily.
  - Quetiapine fumarate 50-100 mg po bid.
- Orient patient as per non-pharmacological recommendations.
- Methotrimeprazine 5-12.5 mg po or 6.25-12.5 mg subcut q4-6h PRN.
- Chlorpromazine 12.5-50 mg po q4-12h PRN.

Moderate and Severe Delirium

Refractory Delirium

NCCN *Modified*

- Palliative sedation is a consideration in refractory delirium and consultation with a palliative care expert or psychiatry is recommended.
- Haloperidol 0.5-2 mg subcut q1h PRN until episode under control; may require a starting dose of 5 mg subcut. Typically, in palliative care, the maximum dose of haloperidol is 20 mg per day.
- Alternate agents:
  - Risperidone 0.5-1 mg po bid.
  - Olanzapine 2.5-15 mg po daily.
  - Quetiapine fumarate 50-100 mg po bid.
- If agitation is refractory to high doses of neuroleptics, consider adding lorazepam 0.5-2 mg subcut q4-6h PRN or midazolam 2.5-5 mg subcut q1-2h PRN and administer in conjunction with the neuroleptic.
- Titrate starting dose to optimal effect.
- Support caregiver.
- Methotrimeprazine 25-50 mg subcut q4-6h PRN.
- Chlorpromazine 25-50 mg po q4-6h PRN.

Drug Therapy for Delirium in Advanced Cancer

☑ The choice of drug therapy must take into consideration the following:

- drug availability,
- familiarity with its use,
- clinical setting,
- patient characteristics,

- environment in which the patient is being cared for.

Refer to Table 4 for specific drug therapy recommendations for delirium in advanced cancer.

Adverse Effects of Medications Used to Treat Delirium

☑ Extrapyramidal side effects (EPS) are common adverse events of neuroleptics, with the newer atypical neuroleptics having a lower risk of EPS than the older typical neuroleptics. Potentially all dopamine antagonists can cause EPS, to varying degrees, due to the D2 central antagonist actions. Manifestations of EPS are usually dose dependent. Extrapyramidal side effects may include: acute dystonia, akathesia, and Parkinson-like signs/symptoms. Akathesia and acute dystonias tend to resolve with discontinuation of the offending drug.

- For the treatment of mild cases one should consider discontinuation of the drug or switching to a less antidopaminergic agent if possible.
- If pharmacologic management is needed, then consider benztropine (1st line) 1-2 mg po/subcut bid (or 2mg IM/IV for acute dystonic reactions).
- Alternative medications include biperiden 2 mg po bid or diphenhydramine 25-50 mg po/subcut bid to qid (or 25-50 mg IV/IM for acute dystonia).

Table 4: Drug Therapy for Delirium in Advanced Cancer (13,23-28)

Drug Class	Drug Name	Mechanism of Action	Route	Dose Range	Frequency	Side effects	Drug Interactions	Comments
Neuroleptic	Haloperidol	D_2 dopamine antagonist	PO Subcut* (*preferred parenteral route) IV	Mild 0.5–1.5 mg Moderate 2– 5 mg Severe 10 mg subcut Maximum usually 20–30 mg per 24h	q8-12h and q1h PRN Titration for severe delirium q30-60 min to achieve effect. For maintenance dose consider 50% of amount required to achieve effect - give daily in 1-3 divided doses.	Less sedating. extrapyramidal (EPS), akathesia (pacing, restlessness), rigidity QT interval prolongation	Substrate CYP2D6, CYP1A2 Inhibits CYP2D6 (paroxetine, methadone), CYP3A4 (methadone)	Considered the Gold Standard Dosing of haloperidol in treatment of delirium is titrated to effect.
	Methotrimeprazine	D_2 dopamine antagonist, $Alpha_1$ adrenergic, & muscarinic receptors, $5HT_2$ receptors	PO Subcut	Mild 5–12.5 mg Moderate 12.5–25 mg Severe 25–50 mg	q12h and q2h PRN q8-12h and q1h PRN q6 – 8h and q1h PRN	More sedating. Useful if need to avoid benzodiazepines. Anticholinergic Hypotension EPS possible	Inhibits CYP2D6 May decrease effects of CYP2D6 prodrug substrates (codeine, oxycodone, tramadol)	Used when sedation beneficial especially in moderate to severe delirium or if adverse effects experienced with haloperidol.
	Chlorpromazine	D_1, D_2 Dopamine antagonist alpha-adrenergic antagonist, moderate anticholiner-gic, weak antihistaminic and antiserotonergic activities	PO	12.5 – 50 mg	Q4-12h PRN	More sedating. Anticholinergic, extrapyramidal (EPS), akathesia, rigidity, hypotension. QT interval prolongation, agranulocytosis (rare).	Substrate CYP2D6, CYP3A4 CYP2D6/3A4 inducers (i.e. carbamazepine, phenobarbital) or inhibitors (i.e. clarithromycin, itraconazole) may increase or decrease metabolism of chlorpromazine respectively	

Table 4: Drug Therapy for Delirium in Advanced Cancer (13,23-28)

Drug Class	Drug Name	Mechanism of Action	Route	Dose Range	Frequency	Side effects	Drug Interactions	Comments
	Olanzapine	D_1, D_2, D_4 dopamine antagonist, serotonin antagonist, $Alpha_1$ adrenergic, $5HT_2$ receptors	PO tablet Oral dissolving wafer	Initial dose 2.5 – 5 mg Maximum 20 mg / day	daily – bid	Sedating Anticholinergic Hypotension EPS possible Diabetes with long term use.	Substrate of CYP1A2, CYP2D6 Inhibits CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4	Mild to moderate delirium only
	Risperidone	D_1, D_2, D_4 dopamine antagonist, serotonin antagonist, $Alpha_1$ adrenergic, $5HT_2$ receptors	PO	Mild 0.5–1 mg Moderate 1–3 mg	daily – bid	Less sedating Non-muscarinic	Substrate CYP2D6, CYP3A4 Inhibits CYP2D6, CYP3A4	Mild to moderate delirium only
	Quetiapine fumarate		PO	Initial 25 mg / day Maximum 300 mg	daily – bid	Anticholinergic Hypotension EPS possible Sedating	Substrate CYP2D6, CYP3A4	Mild to moderate delirium only
Benzodiazepine	Lorazepam	Potentiates the effects of endogenous GABA (inhibitory neurotrans-mitter), principally CNS GABA receptors	PO SL Subcut IV PR	1–4 mg	1-2 mg po / subcut q4-8h and q1h PRN	Sedation Amnesia Respiratory depression Paradoxical reaction seen with benzodiazepines – can increase agitation		Use as additional agent (with neuroleptic) for severe or ongoing intractable delirium in order to sedate. Drug of first choice for delirium caused by alcohol withdrawal.

Table 4: Drug Therapy for Delirium in Advanced Cancer (13,23-28)

Drug Class	Drug Name	Mechanism of Action	Route	Dose Range	Frequency	Side effects	Drug Interactions	Comments
	Midazolam	Potentiates the effects of endogenous GABA (inhibitory neurotrans-mitter), principally CNS GABA receptors	Subcut IV	2.5–5 mg	q30 minutes PRN Can be given as continuous infusion with bolus dose of 2.5 to 5 mg. Then commence infusion rate of 0.5 mg/h, titrate up to effect, to a max of 4 mg/h. If desired effect not obtained recommend referral to Palliative Care physician.	Sedation Paradoxical reaction seen with benzodiazepines – can increase agitation	Substrate CYP2B6, CYP3A4 Inhibits CYP2C8, CYP2C9, CYP3A4	Use as additional agent (with neuroleptic) for severe or ongoing intractable delirium in order to sedate. Drug of first choice for delirium caused from alcohol withdrawal.
Psychostimulant	Methylphenidate	Mild CNS stimulant, blocks reuptake of Norepine-phrine and dopamine presynaptic neurons	PO	Hypoactive delirium 2.5–5 mg	daily or bid (0800 and 1200 hrs) maximum 10 mg/day	Use with caution, risk of shift to hyperactive delirium. Caution in patients with dementia. Caution in patients with serious cardiac abnormalities (cardiomyopathy, arrhythmia) as higher risk of sudden death.	Inhibits CYP2D6	

Note: ACCC= Association of Comprehensive Cancer Centres; bid= twice daily; CNS= Central Nervous System; h= hour; IV= Intravenous; mg = milligrams; NCCN= *National Comprehensive Cancer Network;* PO= per os, by mouth; q=every; PRN = as required; Subcut= subcutaneous; tid= thrice daily

Appendices

Appendix A - Methodology

The Standards, Guidelines and Indicators Sub-group of the Re-Balance Focus Action Group, established under the Canadian Cancer Control Strategy, performed a literature review and environmental scan.[i] This review was used by the SMG as a source from which to identify existing guidelines relative to the four symptoms of interest. Additionally, SMG members reached programs in Ontario, searched the Cancer Care Ontario Program in Evidence-based website and their own personal sources for any relevant guidelines.

The Re-Balanced Focus Action Group used the following search criteria in their review:

Inclusion Criteria

1. Standards focused on care delivered by cancer organizations; and/or processes of care; and/or professional practice standards specific to cancer.
2. Guidelines focused on clinical practice of practitioners relevant to psychosocial, supportive or palliative care provision to cancer patient populations.
3. Guidelines that were more generic in focus but relevant to supportive care aspects of cancer populations in areas such as prevention and screening were also included.

Exclusion Criteria

1. Guidelines that did not base the development of substantive statements/recommendations on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.
2. Guidelines that were focused on providing direction to patients and families for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.

Databases Searched

Health Sciences literature databases used in this scan include HealthStar, Medline, CINHAL, Embase and PsycINFO. The internet search engine Google Scholar was utilized for the grey literature search for scientific and non-scientific sources. Databases for the following organizations were also reviewed: a) All oncology professional associations and organizations for Psychosocial Oncology and Palliative Care inclusive of Oncology Social Workers, Clinical Oncology; b) All Canadian Provincial Cancer Care Organizations within provinces; c) International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development. The literature search and environmental scan was updated in December 2008 and again in January 2009.

[i] Re-Balance Focus Action Group. Literature Review and Environmental Scan: Psychosocial, Supportive and Palliative Care Standards and Guidelines. Updated 2009.

Results

Based on the literature review and environmental scan described above, the Delirium SMG identified six delirium related guidelines for inclusion in this Guide-to-Practice. Two guidelines (29,30) were rejected at the onset by the group because they fell outside of the scope of the Guides-to-Practice or were not methodologically sound. The remaining four guidelines (1-3,31) were screened and assessed for quality, currency, content, consistency, and acceptability/applicability, using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (www.agreetrust.com). Taking into consideration the AGREE scores and expert consensus, the working group chose the most applicable and relevant guidelines (1-3) to be included in the Guide-to-Practice (Table 5).

Table 5. AGREE Scores

AGREE Scores	Fraser Health (1)	Capital Health (2)	NCCN (3)	RNAO (31)
Scope & Purpose	77.78 %	55.56 %	85.19 %	77.78 %
Stakeholder Involvement	43.06 %	40.00 %	41.67 %	54.17 %
Rigour of Development	68.25 %	23.81 %	38.10 %	86.90 %
Clarity & Presentation	75.00 %	65.00 %	77.78 %	87.50 %
Acceptability	27.78 %	8.89 %	22.22 %	52.78 %
Editorial Independence	25.00 %	10.00 %	77.78 %	62.5 %
Overall Quality Assessment	Recommend with provisos. Good generally, well written. Literature search could have been more comprehensive.	Recommend with provisos.	Recommend with provisos. Drugs described are not used in Ontario; good to see antipsychotics were used as they are often more effective; did not specify when meds should be used.	Rejected. Not for this group's perspective; needs more pharmacological recommendations to treat delirium.

The ADAPTE process (http://www.adapte.org/) was then used to systematically endorse or modify applicable components of the three guidelines (1-3). The guideline development process, utilizing ADAPTE, proceeds under the assumption that the original recommendations are reasonable and supported by the evidence. Confidence in this assumption is fostered from satisfactory AGREE scores. In situations were evidence was not available or not applicable to specific clinical situations, systems and contexts recommendations were modified based on the expert consensus of the working group. It is beyond the scope of the Guide-to-Practice development process and this document to make the connection between the recommendations and the original key evidence. For those who wish to do so, please refer to the Fraser Health Hospice Palliative Care Program Symptom Guidelines on Delirium and Restlessness (1), Common Questions by Capital Health (2), and the National Comprehensive Cancer Network's (NCCN's) Palliative Care Practice Guidelines: PAL-18 (3).

Appendix B – Peer Review Summary

Expert feedback was obtained through an internal and external review.

Internal Review

The internal review consisted of an anonymous appraisal of the Guides-to-Practice by members from each of the working groups. The intent of this review was to ensure that the development process was methodologically rigourous; the recommendations were supported by the evidence in a transparent way; and that the guide was clinically relevant and applicable to practice. A total of 39 online surveys were collected during the internal review (Table 6). Eight participants completed the delirium Guide-to-Practice survey. The survey feedback was thoroughly reviewed by each of the corresponding working groups and, where appropriate, changes were made.

Table 6. Responses to 14 key questions on the Delirium Internal Review survey (8 respondents)

Question	**Strongly Agree** Percent (Response count)	**Agree** Percent (Response count)	**Disagree** Percent (Response count)	**Strongly Disagree** Percent (Response count)
The methods for formulating the recommendations are clearly described.	12.5% (1)	75% (6)	12.5% (1)	0%
There is an explicit link between the supporting evidence and the recommendations.	12.5% (1)	75% (6)	12.5% (1)	0%
The recommendations are in agreement with my understanding of the evidence.	37.5 % (3)	62.5% (5)	0%	0%
The recommendations are specific and unambiguous.	37.5 % (3)	62.5% (5)	0%	0%
The recommendations are easily identifiable.	25% (2)	75% (6)	0%	0%
The recommendations are achievable.	25% (2)	75% (6)	0%	0%
The health benefits, side effects, and risks have been considered in formulating the recommendations.	12.5 % (1)	87.5% (7)	0%	0%
When applied, the Guide will produce more benefits for patients than harm.	25% (2)	75% (6)	0%	0%
The different options for management of the condition are clearly presented.	25% (2)	62.6% (5)	12.5 % (1)	0%
The Guide is supported with tools for application.	37.5 % (3)	62.5% (5)	0%	0%
The Guide is user friendly.	12.5 % (1)	87.5% (7)	0%	0%
The Guide presents a series of options that can be implemented.	12.5 % (1)	87.5% (7)	0%	0%

Question	**Yes, Strongly Agree** Percent (Response count)	**No, Strongly Disagree** Percent (Response count)
Do you perceive any barriers or challenges in using this Guide-to-Practice?	12.5 % (1)	87.5% (7)
Would you be able to apply these recommendations to the clinical care decisions for which you are professionally responsible?	100% (8)	0%

External Review

The external review process consisted of: I) a Targeted Peer Review intended to obtain direct feedback on the draft guides from a small number of specified content experts and, II) a Professional Consultation that intended to disseminate the draft guide as widely as possible to its intended readership, provide a forum for recipients to explain any disagreement with the recommendations, and to further ensure the quality and relevance of the document.

I) Target Review

Eight reviewers were invited to participate in the external target review and 6 provided responses (refer to Table 7 and 8 for details).

Table 7. Overview of the Delirium Targeted Peer Reviewers

Guide	Sample	Results
Delirium	**8 Reviewers:** 1 Palliative care physician 1 Psychiatrist 1 Nurse practitioner 3 Pharmacists 2 Methodology experts	**6 Responses:** 1 Palliative care physician 1 Psychiatrist 2 Pharmacists 2 Methodology experts

Table 8. Responses to key questions on the Delirium Peer Review survey (6 respondents)

Question *	1 **Lowest Quality** Percent (Response count)	2 Percent (Response count)	3 Percent (Response count)	4 Percent (Response count)	5 **Highest Quality** Percent (Response count)
Rate the Guide development methods.	0%	0%	17% (1)	50% (3)	17%(1)
Rate the Guide presentation.	0%	0%	33% (2)	67% (4)	0%
Rate the Guide recommendations.	0%	0%	50% (3)	33%(2)	0%
Rate the completeness of the reporting.	0%	17% (1)	17% (1)	50% (3)	0%
Does this document provide sufficient information to inform your decisions?	0%	0%	17%(1)	50% (3)	0%
Rate the overall quality of the Guide.	0%	0%	33% (2)	67% (4)	0%
Question*	1 **Strongly Disagree** Percent (Response count)	2 Percent (Response count)	3 Percent (Response count)	4 Percent (Response count)	5 **Strongly Agree** Percent (Response count)
I would make use of this Guide in my professional decisions.	0%	0%	17%(1)	67% (4)	0%
I would recommend this Guide for use in practice.	0%	0%	17%(1)	33% (2)	33% (2)

*Some participants skipped questions; hence numbers may not add up to 100%

II) Professional Consultation

The Professional Consultation consisted of a sample of approximately 290 health care practitioners. Participants were contacted by email and asked to read the guides and complete a brief corresponding electronic survey. Forty-nine responses were received (Table 9 and 10). Eleven respondents reviewed the Delirium guide.

Table 9. Overview of the Professional Consultation Sample

Profession	Sample	Results
Palliative Care Physicians	49	18
Nurses	32	15
Pharmacists	20	1
Family Physicians	6	4
Medical Oncologists	14	4
Radiation Oncologists	17	1
Surgical Oncologists	11	**0**
Provincial Palliative Care Committee	9	0
Administrative/Researchers	9	3
Dietitians	75	2
Psychiatrists	6	1
Neurologists	16	0
Respirologists	26	0
TOTAL:	**290***	**49 (Response rate 17%)**

* Participant were encouraged to forward the electronic survey to interested colleagues, hence the total sample size is only an estimate.

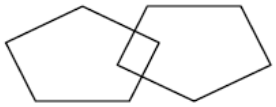
Table 10. Responses to key questions on the Professional Consultation survey (40 respondents)

Question	**1 Strongly Disagree** Percent (Response count)	**2** Percent (Response count)	**3** Percent (Response count)	**4** Percent (Response count)	**5 Strongly Agree** Percent (Response count)
I would make use of this Guide-to-Practice in my professional decisions.	2.1% (1)	2.1% (1)	14.6% (7)	31.2% (15)	50% (24)
I would recommend this Guide-to-Practice for use in practice.	2.1% (1)	2.1% (1)	10.3% (5)	29.2% (14)	56.3%(27)
Question	**1 Lowest Quality** Percent (Response count)	**2** Percent (Response count)	**3** Percent (Response count)	**4** Percent (Response count)	**5 Highest Quality** Percent (Response count)
Rate the overall quality of the Guide-to-Practice.	0	2.1% (1)	14.6% (7)	35.4% (17)	47.9% (23)

Appendix C - Mini-Mental State Exam (MMSE) (32)

Patient's Name: _____
Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Appendix C (Continued) – Mini-Mental State Exam (MMSE) (33-36)

Instructions for administration and scoring of the MMSE

Orientation (10 points):

• Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.

• Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

• Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.

• After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

• Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.

• If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

• Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

• Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).

• Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.

• 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.

• Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.

• Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.

• Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21 >25	Increased odds of dementia Decreased odds of dementia
Education	21 <23 <24	Abnormal for 8th grade education Abnormal for high school education Abnormal for college education
Severity	24-30 18-23 0-17	No cognitive impairment Mild cognitive impairment Severe cognitive impairment

Appendix D - Confusion Rating Scale (CRS) (37)

Date (month, day, year)			
	Day	Evening	Night
Disorientation			
Inappropriate behaviour			
Inappropriate communication			
Illusions/hallucination			

Diagnostic Interview and Screening using the Confusion Assessment Method (CAM) made on: _____

Interviewer: _____ Results of CAM: _____

Positive for Delirium: _____ Negative for Delirium: _____

Directions

1. Record absence or presence of the four behavioural dimensions of confusion at the end of each 8-hour shift.
2. Consider the night shift to begin at midnight.
3. Use the following definitions:
    a. Disorientation: Verbal or behavioural manifestation of not being oriented to time or place or misperceiving persons in the environment.
    b. Inappropriate behaviour: Behaviour inappropriate to place and/or for the person; e.g., pulling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like.
    c. Inappropriate communication: Communication inappropriate to place and/or for the person; e.g., incoherence, non communicativeness, or unintelligible speech.
    d. Illusion/hallucination: Seeing or hearing things that are not there; distortions of visual objects.
4. Code each of the four behaviours as follows:
    0 - behaviour not present during the shift
    1 - behaviour present at some time during the shift, but mild
    2 - behaviour present at some time during the shift, and pronounced
5. If assessment was impossible during the entire workshift, specify the reason as follows:
    A - Natural sleep
    B - Pharmacological sedation
    C - Stupor or coma
    D - Other reason

Appendix E - Nursing Delirium Screening Scale (Nu-DESC) (38)

Features and descriptions	Symptoms Rating (0-2)		
Time Period: Symptom:	Midnight To 8 AM	8 AM To 4 PM	4 PM To Midnight
I. Disorientation Verbal or behavioural manifestation of not being oriented to time or place or misperceiving persons in the environment			
II. Inappropriate behaviour Behaviour inappropriate to place and/or for the person; e.g., pulling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like.			
III. Inappropriate communication Communication inappropriate to place and/or for the person; e.g., incoherence, noncommunicativeness, nonsensical or unintelligible speech.			
IV. Illusions/Hallucinations Seeing or hearing things that are not there; distortions of visual objects.			
V. Psychomotor retardation Delayed responsiveness, few or no spontaneous actions/words; e.g., when the patient is prodded, reaction is deferred and/or the patient is unarousable.			
Total Score			

Fig. 1. The Nursing Delirium Screening Scale (Nu-DESC). Symptoms are rated from 0 to 2 based on the presence and intensity of each symptom and individual ratings are added to obtain a total score per shift. The first four items of the Nu-DESC are included in the CRS. This table may be reproduced without permission. For clinical use only.

Appendix F - Memorial Delirium Assessment Scale (MDAS) ©1996 (39)

INSTRUCTIONS: Rate the severity of the following symptoms of delirium based on current interaction with subject or assessment of his/her behavior or experience over past several hours (as indicated in each item.)

ITEM 1-REDUCED LEVEL OF CONSCIOUSNESS (AWARENESS):

Rate the patient's current awareness of and interaction with the environment (interviewer, other people/objects in the room; for example, ask patients to describe their surroundings).

□ 0: none (patient spontaneously fully aware of environment and interacts appropriately)

□ 1: mild (patient is unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded strongly; interview is prolonged but not seriously disrupted)

□ 2: moderate (patient is unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; interview is prolonged but not seriously disrupted)

□ 3: severe (patient is unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult-to-impossible, even with maximal prodding)

ITEM 2-DISORIENTATION:

Rate current state by asking the following 10 orientation items: date, month, day, year, season, floor, name of hospital, city, state, and country.

□ 0: none (patient knows 9-10 items)

□ 1: mild (patient knows 7-8 items)

□ 2: moderate (patient knows 5-6 items)

□ 3: severe (patient knows no more than 4 items)

ITEM 3-SHORT-TERM MEMORY IMPAIRMENT:

Rate current state by using repetition and delayed recall of 3 words [patient must immediately repeat and recall words 5 min later after an intervening task. Use alternate sets of 3 words for successive evaluations (for example, apple, table, tomorrow, sky, cigar, justice)].

□ 0: none (all 3 words repeated and recalled)

□ 1: mild (all 3 repeated, patient fails to recall 1)

□ 2: moderate (all 3 repeated, patient fails to recall 2-3)

□ 3: severe (patient fails to repeat 1 or more words)

ITEM 4-IMPAIRED DIGIT SPAN:

Rate current performance by asking subjects to repeat first 3, 4, then 5 digits forward and then 3, then 4 backwards; continue to the next step only if patient succeeds at the previous one.

□ 0: none (patient can do at least 5 numbers forward and 4 backward)

□ 1: mild (patient can do at least 5 numbers forward, 3 backward)

□ 2: moderate (patient can do 4-5 numbers forward, cannot do 3 backward)

□ 3: severe (patient can do no more than 3 numbers forward)

ITEM 5-REDUCED ABILITY TO MAINTAIN AND SHIFT ATTENTION:

As indicated during the interview by questions needing to be rephrased and/or repeated because patient's attention wanders, patient loses track, patient is distracted by outside stimuli or over-absorbed in a task.

 0: none (none of the above; patient maintains and shifts attention normally)
 1: mild (above attentional problems occur once or twice without prolonging the interview)
 2: moderate (above attentional problems occur often, prolonging the interview without seriously disrupting it)
 3: severe (above attentional problems occur constantly, disrupting and making the interview difficult-to-impossible)

ITEM 6-DISORGANIZED THINKING:

As indicated during the interview by rambling, irrelevant, or incoherent speech, or by tangential, circumstantial, or faulty reasoning. Ask patient a somewhat complex question (for example, "Describe your current medical condition.").

 0: none (patient's speech is coherent and goal-directed)
 1: mild (patient's speech is slightly difficult to follow; responses to questions are slightly off target but not so much as to prolong the interview)
 2: moderate (disorganized thoughts or speech are clearly present, such that interview is prolonged but not disrupted)
 3: severe (examination is very difficult or impossible due to disorganized thinking or speech)

ITEM 7-PERCEPTUAL DISTURBANCE:

Misperceptions, illusions, hallucinations inferred from inappropriate behavior during the interview or admitted by subject, as well as those elicited from nurse/family/chart accounts of the past several hours or of the time since last examination.

 0: none (no misperceptions, illusions, or hallucinations)
 1: mild (misperceptions or illusions related to sleep, fleeting hallucinations on 1-2 occasions without inappropriate behavior)
 2: moderate (hallucinations or frequent illusions on several occasions with minimal inappropriate behavior that does not disrupt the interview)
 3: severe (frequent or intense illusions or hallucinations with persistent inappropriate behavior that disrupts the interview or interferes with medical care)

ITEM 8-DELUSIONS:

Rate delusions inferred from inappropriate behavior during the interview or admitted by the patient, as well as delusions elicited from nurse/family/chart accounts of the past several hours or of the time since the previous examination.

 0: none (no evidence of misinterpretations or delusions)
 1: mild (misinterpretations or suspiciousness without clear delusional ideas or inappropriate behavior)
 2: moderate (delusions admitted by the patient or evidenced by his/her behavior that do not or only marginally disrupt the interview or interfere with medical care)
 3: severe (persistent and/or intense delusions resulting in inappropriate behavior, disrupting the interview or seriously interfering with medical care)

ITEM 9-DECREASED OR INCREASED PSYCHOMOTOR ACTIVITY:

Rate activity over past several hours, as well as activity during interview, by circling (a) hypoactive, (b) hyperactive, or (c) elements of both present.

 0: none (normal psychomotor activity)

 a b c 1: mild (hypoactivity is barely noticeable, expressed as slightly slowing of movement. Hyperactivity is barely noticeable or appears as simple restlessness.)

 a b c 2: moderate (hypoactivity is undeniable, with marked reduction in the number of movements or marked slowness of movement; subject rarely spontaneously moves or speaks. Hyperactivity is undeniable, subject moves almost constantly; in both cases, exam is prolonged as a consequence.)

 a b c 3: severe (hypoactivity is severe; patient does not move or speak without prodding or is catatonic. Hyperactivity is severe; patient is constantly moving, overreacts to stimuli, requires surveillance and/or restraint; getting through the exam is difficult or impossible.)

ITEM 10-SLEEP-WAKE CYCLE DISTURBANCE (DISORDER OF AROUSAL):

Rate patient's ability to either sleep or stay awake at the appropriate times. Utilize direct observation during the interview, as well as reports from nurses, family, patient, or charts describing sleep-wake cycle disturbance over the past several hours or since last examination. Use observations of the previous night for morning evaluations only.

 0: none (at night, sleeps well; during the day, has no trouble staying awake)

 1: mild (mild deviation from appropriate sleepfulness and wakefulness states: at night, difficulty falling asleep or transient night awakenings, needs medication to sleep well; during the day, reports periods of drowsiness or, during the interview, is drowsy but can easily fully awaken him/herself)

 2: moderate (moderate deviations from appropriate sleepfulness and wakefulness states: at night, repeated and prolonged night awakening; during the day, reports of frequent and prolonged napping or, during the interview, can only be roused to complete wakefulness by strong stimuli)

 3: severe (severe deviations from appropriate sleepfulness and wakefulness states: at night, sleeplessness; during the day, patient spends most of the time sleeping or, during the interview, cannot be roused to full wakefulness by any stimuli)

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Post-amble

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A wide variety of health professionals were invited to participate in the development of this Guide-to-Practice, as well as in the external review. Every effort was made to ensure as broad a professional and regional representation as possible.

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Conflict of Interest

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