

**Special Section: Studies to Understand Delirium In Palliative Settings (SUNDIPS)**

# An Analytical Framework for Delirium Research in Palliative Care Settings: Integrated Epidemiologic, Clinician-Researcher, and Knowledge User Perspectives

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## Abstract

**Context.** Delirium often presents difficult management challenges in the context of goals of care in palliative care settings.

**Objectives.** The aim was to formulate an analytical framework for further research on delirium in palliative care settings, prioritize the associated research questions, discuss the inherent methodological challenges associated with relevant studies, and outline the next steps in a program of delirium research.

**Methods.** We combined multidisciplinary input from delirium researchers and knowledge users at an international delirium study planning meeting, relevant literature searches, focused input of epidemiologic expertise, and a meeting participant and coauthor survey to formulate a conceptual research framework and prioritize research questions.

**Results.** Our proposed framework incorporates three main groups of research questions: the first was predominantly epidemiologic, such as delirium occurrence rates, risk factor evaluation, screening, and diagnosis; the second covers pragmatic management questions; and the third relates to the development of predictive models for delirium outcomes. Based on aggregated survey responses to each research question or domain, the combined modal ratings of “very” or “extremely” important confirmed their priority.

**Conclusion.** Using an analytical framework to represent the full clinical care pathway of delirium in palliative care settings, we identified multiple knowledge gaps in relation to the occurrence rates, assessment, management, and outcome prediction of delirium in this population. The knowledge synthesis generated from adequately powered, multicenter studies to answer the framework’s research questions will inform decision making and policy development regarding delirium detection and management and thus help to achieve better outcomes for patients in palliative care settings. *J Pain Symptom Manage* 2014;48:159–175. © 2014 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

## Key Words

*Delirium, palliative care, risk factors, decision making, hospice, research framework, assessment, treatment, predictive model*

## Introduction

### *Delirium in Palliative Care: A Research Priority*

Delirium is one of the most common neuropsychiatric complications in patients who are receiving palliative care. A recent epidemiologic review, based on a small number of eligible studies conducted in inpatient palliative care units, reported a delirium prevalence of 13%–88% and an incidence of 3%–45%, where collectively 98.9% of the study samples had a cancer diagnosis.<sup>1</sup> These wide ranges are likely due to variation across the included studies in delirium diagnostic criteria, levels of assessment, frequency of screening, and proximity to death. Despite this high frequency

of delirium, it is remarkably underresearched in the settings of palliative care.<sup>1–3</sup> The paucity of research may relate in part to the challenging and potentially elusive nature of delirium in itself and also to complexities arguably specific to palliative care.<sup>3–5</sup> An awareness of the contextual complexities of palliative care and the settings in which it is delivered, as well as determining the specific palliative care populations to study, is a prerequisite for formulating meaningful and patient-centered research questions in investigating the interface of delirium and palliative care.

Despite widening the definition of palliative care to include “life threatening disease”<sup>6</sup> and aside from some geographical and health-care

system exceptions, most patients in palliative care settings have advanced cancer.<sup>7,8</sup> The growth in demand for palliative care in the developed world over the past decade relates to changing population demographics, such as the increase in the proportion of elderly persons,<sup>9,10</sup> and the associated increase in the number of cancer-related deaths in this population.<sup>11,12</sup> The expanded role of palliative care services is now reflected by the delivery of palliative care in multiple settings: specialist inpatient units, including those in stand-alone hospices and acute care settings; hospital consult teams; and community palliative support teams.<sup>13–15</sup> Collectively, given the strength of advanced age and dementia as risk factors for delirium;<sup>16</sup> the propensity for delirium to occur in the cancer trajectory, especially in the advanced stages;<sup>1,17</sup> and combined with the projected population demographic changes in developed countries, it is clear that delirium will have an increasingly ubiquitous presence in the entire remit of palliative care and thus constitutes a research priority.

#### *Clinical Trajectory of Delirium in Palliative Care: A Case Vignette*

Various agencies that commission or conduct clinical research use an analytical framework, typically based on clinical trajectories, to strategically guide the development process of generating research questions.<sup>18–20</sup> To illustrate the complex clinical pathway of delirium in palliative care, we present a hypothetical though typical case vignette of a patient with advanced cancer, “Frank,” who experiences two recognized episodes of delirium during his eight months trajectory with lung cancer (Table 1). This case highlights some of the contextual issues in palliative care relating to assessment, diagnosis, management, impact, and outcome of delirium.

#### *Delirium Assessment and Diagnostic Issues*

The clinical manifestations of delirium in the palliative care population may vary widely and thus present some unique diagnostic and classification challenges.<sup>17,21</sup> The *Diagnostic and Statistical Manual* (DSM) of the American Psychiatric Association has been the mainstay in generating diagnostic criteria for delirium,

and the 5th edition, DSM-5, has recently been published (Table 2).<sup>22</sup> Delirium is characterized by an acute and fluctuating impairment of attention and awareness, in addition to other cognitive deficits such as perceptual disturbances or memory impairment. Cognitive impairment as part of a delirium or other mild or major neurocognitive disorders is highly prevalent in hospice and palliative care settings and frequently missed.<sup>23,24</sup> Tests such as the Short Orientation and Memory Concentration Test<sup>25</sup> act as a crude screen for cognitive impairment, regardless of its associations, and in Frank’s case, the impairment was associated with delirium. In addition to cognitive deficits, the Confusion Assessment Method (CAM)<sup>26</sup> captured other features of delirium in Frank’s case, such as acute onset and fluctuating course.

Based on psychomotor status aberrations, delirium is classified into hyperactive (hyper-alert and often agitated), hypoactive (hypo-alert and often somnolent), or mixed (features of both hypo- and hyperactive) subtypes. In Frank’s case, he presented with the mixed subtype; its features were associated with a perceived need for an early visit to the hospital emergency department. However, the hypoactive subtype has been reported as the most common in palliative care and is also the subtype that is prone to misdiagnosis as depression or fatigue in this setting.<sup>21</sup> Fluctuation in the intensity and nature of the clinical manifestations of delirium, including psychomotor hypoactivity, can result in missing the diagnosis, and screening has therefore been advocated in palliative care.<sup>1,27</sup> However, an optimal screening strategy for delirium in palliative care settings that balances burden and benefit has been neither evaluated nor defined.

#### *Delirium Management Issues*

Episodes of delirium are invariably multifactorial in origin and typically involve acute precipitating factors—such as infection, hypercalcemia, and dehydration—as in Frank’s first episode of delirium—superimposed on a background of baseline vulnerability, for example, advanced age, advanced disease with multiorgan dysfunction, or dementia.<sup>28–30</sup> Although the potential reversibility of delirium has been demonstrated in many settings,<sup>29,31,32</sup>

Table 1  
Case Vignette of Delirium in the Clinical Trajectory of Advanced Cancer

Context	Description
Precancer	Frank, a 72-year-old man, lived with his 70-year-old wife in a two-storey suburban home. He was ambulatory and independent in activities of daily living. There were no reported cognitive deficits.
Cancer diagnosis	Eight months ago, he was diagnosed with non-small-cell (squamous cell) lung cancer
Staging and management	Locoregional, Stage III B. ECOG performance status = 1. Despite a partial response to initial concurrent chemoradiation, he became progressively weaker, and his chemotherapy was discontinued three months ago.
1st episode of delirium	<ul style="list-style-type: none"> <li>• Two months ago</li> </ul>
Presentation	Brought to the hospital emergency room with acute-onset cognitive impairment, behavioral disturbance, and two near falls in the preceding 48 hours.
Clinical history	Dozing off during conversation, daytime sleepiness but awake and restless all night, and at times appeared to have visual hallucinations. Vague complaints of upper abdominal pain. Increasing respiratory distress over the preceding two days.
Cognitive and behavioral assessment	Scored 15/28 (normal <6) on Short Orientation and Memory Concentration Test (SOMCT). Confusion Assessment Method (CAM) testing was positive for delirium. Mixed hyperactive and hypoactive psychomotor features of delirium were noted.
Decision-making and palliative care support	Potential delirium treatment strategies were discussed with his wife as the substitute decision maker. She initially did not want added investigational or therapeutic burden on Frank because of intravenous lines or the possibility of antibiotic side effects without some gain in his quality of life, yet she dearly wished for more time for him. Ultimately, the consensus was to investigate and treat his delirium.
Investigations	Hypercalcemia noted. Consolidation, consistent with pneumonia on chest imaging.
Treatment	Delirium precipitant treatment: intravenous fluid, antibiotics, and zoledronic acid. Symptomatic treatment of delirium: regularly scheduled and as needed haloperidol.
Outcome	Frank's delirium largely reversed over three days. Cancer restaging revealed hepatic and adrenal metastases (Stage IV) but no brain metastases. His ECOG status had now deteriorated to three. He was discharged home under the care of his family physician and the community palliative care team.
2nd episode of delirium	<ul style="list-style-type: none"> <li>• One month ago</li> </ul>
Summary	Despite worsening fatigue and episodic mild cognitive deficits, he remained at home for four weeks before developing another episode of delirium. The likelihood of recurrent hypercalcemia was discussed with his family, but as their wish at this point was for solely comfort care without any further blood work, this episode of delirium was not investigated. Because of family exhaustion and concern about inadequate pain control, Frank was admitted to a local inpatient hospice unit, where he received subcutaneous morphine to control his pain and low-dose midazolam to control symptoms of delirium before his death seven days later.

ECOG = Eastern Cooperative Oncology Group.

including palliative care,<sup>29,30</sup> though nonreversal is clearly recognized as a frequent outcome in the context of palliative care.<sup>29,33</sup> The reversibility of delirium in this patient population, and the extent to which this can be predicted, is a major research priority.<sup>3</sup> If consistent with the agreed goals of care, the standard approach in palliative care is to identify and treat modifiable precipitant factors.<sup>17,34–36</sup> As delirium frequently accompanies the terminal phase of illness in palliative care settings, there is a risk that some potentially reversible episodes may be

overlooked or prematurely perceived as terminal.<sup>3,17</sup> Conversely, there is the risk that overly aggressive medical interventions can be applied in nonreversible episodes of delirium. Thus, the reversibility of a particular episode of delirium may present a clinical dilemma for the clinician regarding how aggressively to pursue reversal and has the potential for substantive agonizing on the part of the substitute decision makers, with the goals of care often predicated on substantive uncertainty about the potential for delirium reversal. This decision-making challenge is also

Table 2

**Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Diagnostic Criteria for Delirium**

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- A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
- C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
- D. The disturbances in Criteria A and C are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
- E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or a medication), or exposure to a toxin, or is due to multiple etiologies
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compounded by legitimate concerns of substitute decision makers, such as Frank's wife, about the predicted benefit vs. burden of investigation and consequent treatment of identified delirium precipitants. Comparatively, in the case of Frank's second episode of delirium, his now known expressed wishes to not have further investigations meant that therapeutic decision making was clearer. Yet an individualized approach is still warranted, especially as treatment of his first delirium episode gave him the opportunity to have a month at home with his family.

*Delirium Impact and Outcome Issues*

Delirium is a distressing experience primarily for the patient but also for the family.<sup>37-42</sup> It impedes meaningful and highly valued communication sometimes in a preciously narrow temporal window. Furthermore, delirium may compromise the quality of pain and other symptom assessments by health-care personnel. Apart from the distressed decision making during the first delirium episode, other notable aspects of Frank's case include his symptomatic distress; his fall risk; reversal of the first delirium episode with relatively low burden interventions such as assisted hydration, antibiotics, and bisphosphonate treatment; family burden; and the major difficulty in assessing pain in the context of delirium.

*Objectives*

The combined complexities of the delirium syndrome and the palliative care context pose significant challenges for the researcher, yet for future improved patient and family outcomes, it is imperative to address the gaps in clinical research. Reflecting the trajectory issues identified in our case vignette, the

objectives of this article are to 1) formulate an analytical framework for further research on delirium, based on a conventional clinical approach in palliative care, 2) report a preliminary level of priority to the research questions arising from this analytical framework, 3) discuss the inherent methodological challenges associated with studies designed to answer the framework questions and propose solutions, and 4) outline the next steps in our program of research.

*Methods*

We developed a provisional analytical framework depicting the clinical care pathway of delirium in palliative care. Grounded in decision theory, analytical frameworks are useful in understanding the context and logic with which clinical decisions are made or should be made. Such frameworks are routinely used in developing research questions or agenda, so that once answered by evidence, decision and policy makers are convinced of the comparative effectiveness, harms, and cost-effectiveness of alternative management options.<sup>18,19,43</sup> Using an analytical framework to articulate questions of research interest minimizes investigator bias in the conception of research, reveals previous beliefs and assumptions that are not evidence based, and imparts patient-centered dimension to the research and associated decision making.

As an integral part of the process in developing an analytical framework for delirium research in the palliative care population, we obtained multidisciplinary input from leading delirium researchers, methodologists, primary care and specialist-level clinicians, palliative

care experts, and clinical administrators at an international two day delirium study planning meeting in Ottawa, Canada, in June 2012.<sup>44</sup> Our meeting was designed to promote collaboration and initiate deliberations toward the development of a research framework under the broad heading of “Studies to Understand Delirium In Palliative Settings” and hence the acronym, SUNDIPS. Within this broad SUNDIPS program of research, we targeted three major investigational domains for delirium in palliative care settings as subprograms of research: 1) epidemiologic issues and issues of delirium prediction, screening, and diagnosis, 2) experiential or phenomenologic aspects of delirium in its entire trajectory, including subsyndromal and full syndromal states, and 3) comparative effectiveness of alternative management strategies in established delirium. All presentations and interactions during the sessional working groups were recorded and transcribed. The results of systematic literature searches in relation to the subprograms of research are described in their corresponding articles in this section.<sup>45–50</sup>

By integrating knowledge users and engaging them in the consultative and collaborative process at this meeting, we aimed to address the specific contextual sensitivities, needs, and decisional determinants in palliative care and thus help to better inform the rationale and design of future research, knowledge translation, management guidelines, and policy regarding delirium in this setting. The data synthesis from this meeting and the associated literature searches were supplemented by subsequent focused input from coauthors with recognized epidemiologic expertise. Collectively, these inputs informed the formulation of specific research questions at various points in the analytical framework.

Having developed the research questions to populate the research framework, the meeting attendees or coauthors ( $n = 30$ ), with a background of delirium research and clinical experience in palliative care, and those working with patients with advanced cancer were asked to complete an anonymous online pilot survey to assign a preliminary priority level (0 = N/A, not applicable or unable to rate, 1 = not at all important, 2 = slightly important, 3 = moderately important, 4 = very important, and 5 = extremely important) to the research question or groups of questions.

Five standard criteria were used to rate the importance of answering either an individual question or at least one question in a domain, represented by a predetermined group of related questions.<sup>51</sup> The criteria were (A), need to determine the burden and impact of disease in relation to delirium; (B), need to inform decisions in clinical practice where there is controversy or uncertainty; (C), need to estimate the economic cost and/or resource utilization associated with delirium; (D) known need to address this knowledge deficit; and (E) potential impact of the answer on clinical practice. The need for ethics approval for the survey was discussed with our local research ethics board, but given that the raters were either participants ( $n = 26$ ) in the SUNDIPS meeting with a clearly informed objective of developing a research agenda or subsequently enlisted as coauthors ( $n = 4$ ) for this purpose, formal research ethics board application and approval was deemed to be not necessary.

Finally, the reported methodological and other challenges associated with the conduct of studies in the research framework, their proposed respective solutions, and an outline of the next steps to advance the overall SUNDIPS program of research were derived in part from the SUNDIPS meeting and in part from subsequent focused input of epidemiologists and other coauthors.

## **Results and Discussion**

### *Formulation of an Analytical Framework and Pertinent Research Questions*

The analytical framework developed by our team for delirium research in palliative care settings is presented in [Figure 1](#). The individual research questions populating the entire framework are labeled Q1–Q18. These questions are divided into three groups, each reflecting a major domain with an associated overall research goal or set of goals. We broadly discuss each group, acknowledging that an in-depth discussion of each specific question is beyond the scope of this article. Questions cover a spectrum of inquiries ranging from the prevalence of delirium in various palliative care settings to comparative test performance, their effectiveness and harms, resource utilization, and incremental costs when incorporated in patient management strategies. The left half of the

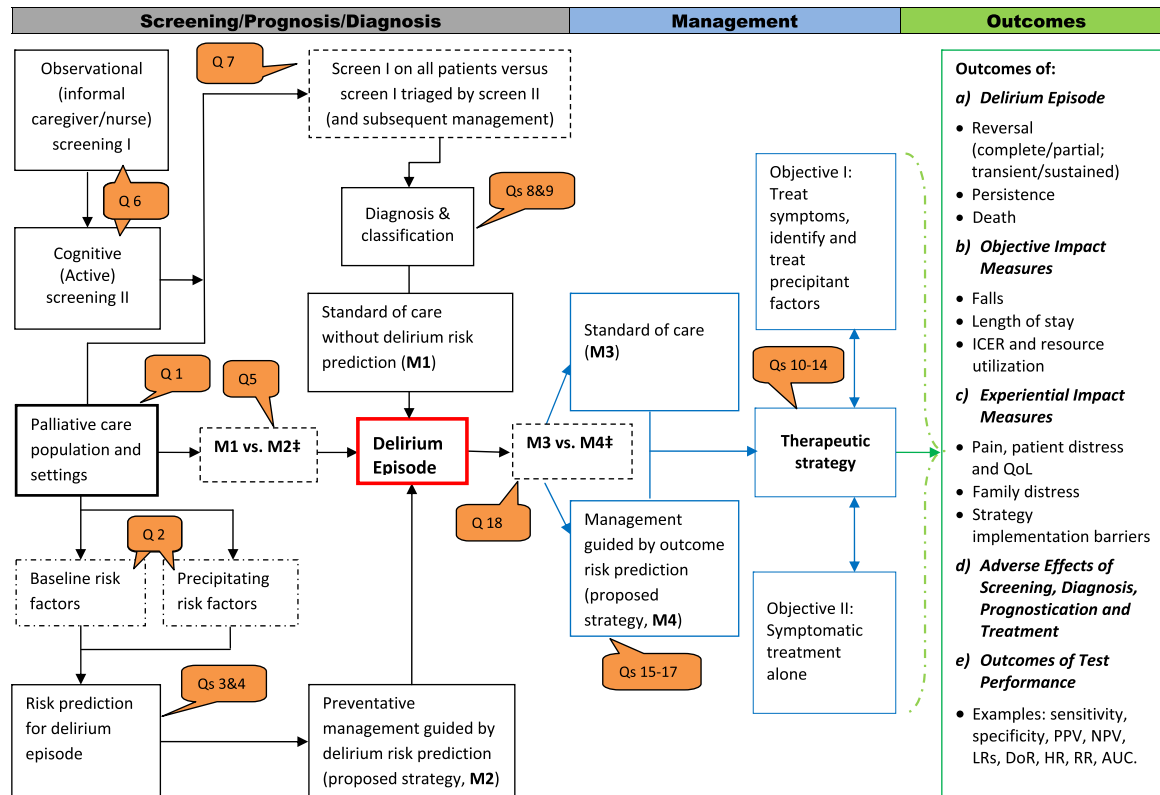


Fig. 1. Analytical framework for research questions on delirium in palliative care settings. Boxes with broken lines are not steps in the care pathway but describe either a relevant clinical equipoise or determinants of a pathway step. ‡M1 and M2 are pre-delirium management strategies; M3 and M4 are strategies to manage established delirium. ICER = incremental cost-effectiveness ratio; QoL = quality of life; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; DoR = diagnostic odds ratio; HR = hazard ratio; RR = risk ratio; AUC = area under the curve.

framework in Figure 1 depicts the care pathway (and related questions) up to the onset of delirium, whereas the right half displays the pathway once delirium diagnosis is established.

Many of the questions arise at pivotal decision points in the clinical care pathway where, in the absence of evidence, there are substantive reported differences in management,<sup>52</sup> or where clinical equipoise exists in relation to the choice between alternative management options, for example, outcomes based on the current standard management compared with those with management directed by a risk prediction model. We also prespecified a select number of outcomes that are considered important for decision making, including incremental cost-effectiveness and resource utilization.

The first group of questions (Q1–Q9) is presented in Table 3 and addresses the burden of delirium in terms of its occurrence rates, risk factor evaluation, screening, and diagnosis

and is thus predominantly epidemiologic in nature. Hosie et al.<sup>1</sup> reported a systematic review of delirium incidence and prevalence in inpatient palliative care units; however, few data exist to allow comparison across other palliative care settings. Although risk factors for delirium have been identified across a wide variety of medical settings<sup>16,53</sup> and the efficacy of some prevention strategies has been clearly proven,<sup>54–56</sup> data from palliative care settings have been limited and thus far a single prevention study with substantive recognized methodological limitations failed to show benefit.<sup>57</sup> The negative outcome with this study should not preclude future more rigorously designed studies in the palliative care population. Apart from psychoactive medications, the identification of risk factors in a small number of studies, conducted in either palliative or cancer care settings, has been somewhat inconsistent.<sup>29,30,58–63</sup>

Table 3

**Research Questions (Q1–Q9) of Analytical Framework for Delirium Research in Palliative Care Settings**

## Occurrence rates and burden of delirium

1. What are the incidences and prevalence rates of delirium in the various palliative care settings (acute care, inpatient hospice and hospital care, and community palliative services)?

## Delirium prediction

2. What are the baseline and precipitating risk factors for the onset of delirium?
3. Which is the most parsimonious delirium risk prediction model with the highest calibration and discrimination value under the current standards of care?
4. Does the model have transportability or external validity?
5. What are the comparative effectiveness and harms of the high-performance risk prediction model(s) in reducing the incidence of delirium and important delirium-associated outcomes? (i.e., what are the comparative effectiveness and harms of delirium-preventative management strategies guided by risk prediction as opposed to the current standards of care?)

## Screening for delirium

6. What is the test performance of cognitive active screening for delirium vs. nurse/informal caregiver observational passive screening?
7. What are the comparative effectiveness and harms of cognitive active screening of all patients vs. cognitive active screening triaged by nurse/informal caregiver observational passive screening for important delirium-associated outcomes?

## Diagnosis of delirium

8. What are the comparative diagnostic performance and applicability limitations of the various validated delirium diagnostic tools (in current use)?
9. What are the comparative effectiveness and harms of the various validated delirium diagnostic tools (in current use) for important delirium-associated outcomes?

Can we develop a predictive model for incident delirium in palliative care? The purpose of such a model would be to identify persons at greatest risk of delirium. Pragmatically, the question can be primarily focused in relation to individuals at the point of admission to inpatient or community palliative care services. The basis of the model would be a prospective observational cohort study examining baseline and precipitating risk factors for incident delirium. Apart from “subsyndromal” delirium and other potential prodromal clinical predictors,<sup>64,65</sup> a prediction model might explore the potential predictive role for biomarkers such as cytokines, insulin-like growth factor-1, cortisol, and C-reactive protein, though inconsistent findings have been noted to date.<sup>61,66–70</sup> Such studies will need careful attention to how putative biomarkers otherwise correlate with disease stage if their associations with delirium (over and above disease stage) are to be understood. A fundamental construct of predictive models in delirium is the understanding that predisposing factors (baseline risk) and precipitating factors (illness severity) interact in a reciprocal fashion.<sup>28,53</sup> Accordingly, relatively minor intercurrent illness can result in delirium in older frail persons, whereas more severe acute illness is necessary to produce delirium in younger individuals. If such a model could

generate a risk prediction score in a manner similar to the PRE-DELIRIC model for intensive care units,<sup>71</sup> it might be used to guide early preventative interventions in delirium and predict resource utilization. It could also form the basis of power calculations in future randomized controlled trials.

Although screening has been advocated in palliative care settings, there are limited literature data on its evaluation.<sup>1</sup> Also, there is little evidence with which to compare the efficacy of a cognitive screening tool requiring active patient participation, such as the Mini-Mental State Examination<sup>72</sup> or Short Orientation and Memory Concentration Test, vs. a nurse-rated observational tool, such as the Nursing Delirium Screening Scale, though clearly the latter is less burdensome in a vulnerable population with advanced disease.<sup>45,73,74</sup> A recent study suggests that caregiver observations may detect prodromal delirium features, especially sleep disturbance, a finding that warrants further evaluation.<sup>75</sup> Also, use of the CAM by family members (FAM-CAM) has demonstrated high levels of sensitivity and specificity.<sup>76</sup> Earlier diagnosis of delirium (M2 in Fig. 1) could conceivably lead to earlier therapeutic intervention and thus potentially lessen distress, whether the goals of care (Therapeutic Strategy in Fig. 1) might be directed toward either comfort and symptomatic

treatment alone (Objective I in Fig. 1) or symptomatic treatment in combination with treatment of precipitant factors (Objective II in Fig. 1). Although many assessment tools have been developed and validated, apart from the CAM,<sup>77</sup> they have been exposed to limited validation in the palliative care population.<sup>45</sup> Diagnostic challenges and outcome measures in relation to subsyndromal delirium, delirium superimposed on dementia, and the psychomotor subtypes are addressed separately.<sup>47</sup>

The second group of research questions (Q10–Q14) is presented in Table 4; this group largely covers pragmatic management questions, especially in relation to differences across the various palliative care settings, and would entail longitudinal observational studies. A retrospective study of delirium documentation and management in hospice and hospital patients referred to a palliative care team found that the term “delirium” was used infrequently, but definitive use of the term was associated with clearer management plans in the hospital patients.<sup>27</sup> The group also includes important questions where clinical equipoise exists regarding both pharmacologic and nonpharmacologic interventions and ideally require a randomized controlled study trial design to answer the respective questions. Although comparative studies have been reported regarding pharmacologic agents for symptomatic control in other settings,<sup>48,78,79</sup> few have been conducted in palliative care settings.<sup>48,80</sup>

The third group of questions (Q15–Q18) is presented in Table 5; the questions relate to the development of predictive models for delirium outcomes in response to patient management—particularly the outcome of delirium reversibility. Accordingly, an extension of the delirium risk model (Q2–Q5) would be to further investigate components of delirium risk that might be reversible or

modifiable. The precipitating factors associated with delirium reversal in palliative care settings have been examined in a small number of studies.<sup>29,30,32,33,63</sup> In a study examining delirium reversibility, psychoactive medications, including opioids and benzodiazepines, were independently associated with delirium reversal, and both hypoxic encephalopathy and nonrespiratory infection were independently associated with nonreversal.<sup>29</sup> Given the paucity and inconsistent findings of literature data on risk evaluation and in turn the limited data on reversibility predictors of delirium in palliative care settings, there is a compelling need for a prospective cohort observational study for model development. Unfortunately, because of the poor recognition of delirium and its poor and inconsistent documentation in inpatient settings, research studies to identify predictors through administrative databases are unlikely to be helpful.<sup>81</sup> Furthermore, the external validity of delirium reversibility findings in other care settings such as intensive care is uncertain in relation to palliative care settings.<sup>53</sup>

In summary, in palliative care settings, substantive evidence base deficits exist regarding basic epidemiologic data, therapeutic strategies, and their impact on the many outcome measures of delirium, which poses uncertainty for decision making in everyday clinical practice. Similar to the priorities generally identified in relation to other settings,<sup>53,70,82</sup> there is therefore a compelling need for observational cohort studies and randomized controlled trials to address our proposed research questions in palliative care and consequently inform a number of important outcomes:

- partial or complete reversibility of delirium, and its sustainability, in response to treatment

Table 4

**Research Questions (Q10–Q14) of Analytical Framework for Delirium Research in Palliative Care Settings**

Management of delirium

10. What is the extent of variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services)?
11. Is the variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services) associated with important differences in outcomes of benefit and harms?
12. What are the comparative effectiveness and harms of delirium management strategies that incorporate advanced directives and/or substitute decision maker input vs. those that do not?
13. What are the comparative effectiveness and harms of the various pharmacologic symptom-directed interventions?
14. What are the comparative effectiveness and harms of the various nonpharmacologic symptom-directed interventions?

Table 5

**Research Questions (Q15–Q18) of Analytical Framework for Delirium Research in Palliative Care Settings**

Prediction of response to management and treatment of delirium

15. In patients with established delirium, what are the risk factors that predict complete or partial reversibility of delirium and sustainability of response?
16. Which is the most parsimonious risk prediction model with the highest calibration and discrimination value for predicting complete or partial reversibility of delirium under the current standards of care?
17. Does the model have transportability or external validity?
18. What are the comparative effectiveness and harms of patient management guided by model(s) predicting delirium reversibility vs. current standards of care?

- symptomatic conservative management vs. extensive workup to identify and treat precipitating factors
- tailoring management objectives in light of advanced directives or the agreed goals of care
- cost and resource utilization measures
- risk factor evaluation and evaluation of preventative strategies
- prediction of outcomes such as death; falls; length of stay; patient, family member, and health-care professional distress; quality of life; pain relief; and impact on family member bereavement.

Finally, although the experiential and phenomenologic dimensions of delirium from the patient, family, and health-care personnel perspectives are largely embedded in the outcome measures in [Figure 1](#), their apparently low level of prominence in the framework is disproportionate to their actual perceived level of importance in clinical practice. The inherent complexity associated with these aspects warrants a mixed-methods approach that embodies both qualitative and quantitative methods.<sup>46</sup>

#### *Preliminary Priority Level of Research Questions Based on Survey Results*

The results of a survey of the SUNDIPS meeting attendees and coauthors to assign levels of importance to the research questions are summarized in the bar chart in [Figure 2](#). Twenty-eight of 30 (93%) invited survey participants responded. Rating the research domains and their associated question(s) according to the five criteria of importance (A–E), the 28 survey respondents generated an aggregate total of 140 ratings per domain and an overall total of 840 ratings. Percentages represent the number of categorical ratings out of the total of 140 for each domain.

Responding to the perceived importance of a question or a domain in relation to a specific criterion, “unable to rate or not applicable,” or “not at all important” occurred in only 18 (2%) and 22 (2.6%) of 840 ratings, respectively. The modal response category was very important for each of the domains, except for Q8–Q9 and Q10–Q14, whose modal categories of response were moderately important and extremely important, respectively. In summary, for each research domain or question(s), a post hoc–created combination category of either “very important” or “extremely important” represented the modal response and ranged in frequency from 80.7% for Q10–Q14 to 56.5% for Q6–Q7.

#### *General Methodological Challenges of Studies to Answer the Research Framework Questions*

The challenges can be broadly categorized as relating to the study population and setting, the ascertainment of study outcomes and exposures, and statistical issues in relation to longitudinal data analysis.

*Study Population and Setting.* There are many general challenges in relation to conducting any research in the palliative care population. Patients in palliative care settings have advanced disease, mostly advanced cancer, and frequent comorbidities. Conducting delirium research in the advanced cancer population or in any end-of-life condition is challenging because of patient vulnerability, ethical issues around informed consent, and willingness of patients to participate in research, often resulting in limited patient accrual to studies and high attrition rates in those who are recruited.<sup>3–5</sup> The ethical challenges and possible solutions are discussed separately in this section.<sup>50</sup> The recruitment and attrition issues are challenging for most centers, making multicenter collaboration

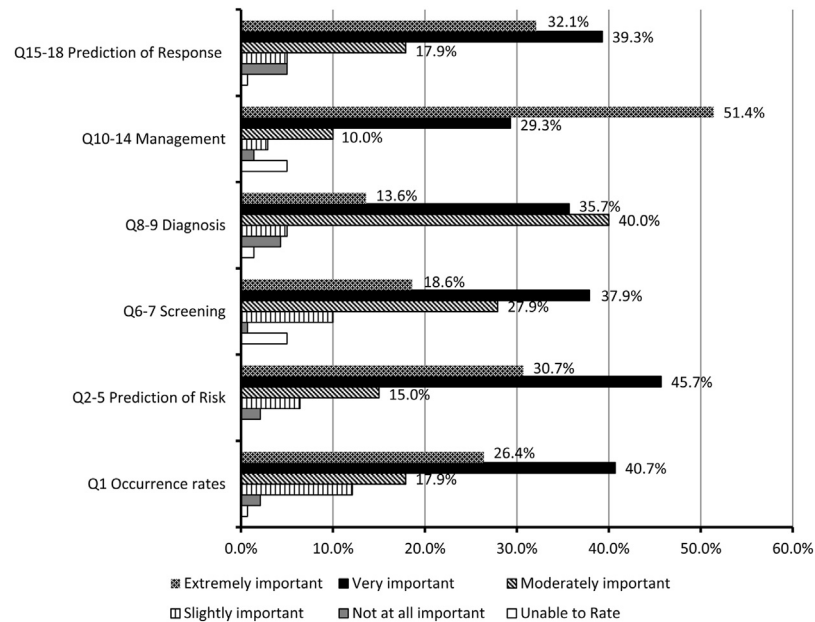


Fig. 2. Aggregate results of importance survey on research questions (Q1–Q18) from the analytical framework. Each of the six question (Q) domains was rated according to five criteria of importance (A–E) by 28 survey participants to give an aggregate total of 140 ratings per domain. Percentages represent the number of categorical ratings out of the total of 140 for each domain.

almost an essential requirement so as to conduct adequately powered studies.<sup>83,84</sup> In turn, this necessitates agreement on commonality of assessment tools and procedures across sites, including eligibility criteria. To broadly represent the palliative care population, there is an ethical and equity-based argument for an inclusive approach that would include a growing proportion with nonmalignant end-of-life illnesses. However, the consequent heterogeneity creates challenges for statistical analysis, especially in relation to predictive models, whereas the homogeneity associated with an exclusive selection of a cancer diagnosis for eligibility supports a more powerful analysis. Larger sample sizes would allow stratification in relation to malignant and nonmalignant diagnoses and also in relation to the presence or absence of pre-existing dementia.

With an initial aim to generate robust predictive models, the study population of primary interest will most likely be defined as persons with a cancer diagnosis, at least initially. Given the desirability of ease of access to investigative procedures, the predominant care setting for recruitment will likely be an inpatient palliative care unit, such as a hospice or hospital-based unit. Combining sites to

recruit such a population will encounter heterogeneity issues, including varying criteria for admission to inpatient palliative care units, variation in disease staging and performance status, variation in the agreed goals of care, and site availability of investigative procedures, cancer treatments, and other services, for example, psychiatry or palliative care consultation. Accordingly, the multiple constructs contributing to heterogeneity will need to be meaningfully and rigorously defined and the consequent stratifications accounted for in the analyses. Some community-based palliative care teams have sufficient access to laboratory services to allow basic delirium investigation, and combining this with emergency room data and standardized caregiver reporting, may possibly be the only way of optimally capturing data on delirium in the community setting.

*Ascertainment of Outcomes and Exposures.* The primary reference standard used in delirium research is the DSM criteria, recently published as the 5th edition, DSM-5 (Table 1).<sup>22</sup> As with many syndromes in psychiatric epidemiology, the boundaries of the diagnosis are difficult to define consistently across assessors and across

sites.<sup>85</sup> Moreover, if an instrument is used for screening and/or case ascertainment, multiple sources for the propagation of misclassification biases result in substantial losses of statistical power. Standardized procedures such as a semi-structured interview to operationalize the DSM-5 diagnostic criteria are necessary.

There is a trade-off between intensity of assessment schedules (and necessary expertise) for study personnel and the ability to assess large numbers of participants. At one extreme, assessment and diagnosis might be performed at the same time, for example, using the gold standard of a psychiatrist interview. This has the advantage of expert case ascertainment at each assessment but is potentially resource intensive. Alternatively, a two-stage approach might involve a screening test done more frequently by personnel with less expertise, with ascertainment performed in screen positives by an experienced palliative care practitioner. At each stage, it would be essential to assess a random sample of screen negatives. Consequently, targeted use of expert ascertainment would be more efficient, but the separation of the screening and ascertainment processes may be a problem given temporal fluctuations in delirium. Clearly, the study protocol should stipulate an optimal gap between screen and ascertainment. It would be ideal to choose screening instruments or structured assessment protocols with established diagnostic properties (sensitivity and specificity) and thus validated in palliative care settings. The lead-in to any epidemiologic study should include an assessment of diagnostic accuracy of the instruments within the study. Ethically, the burden of assessment procedures, as reflected by their duration and/or intensiveness and consequent acceptability to participants, must be considered.<sup>50</sup> Inability to rate specific items in severity-measuring tools may require prorating of the total score based on those items that were rateable.<sup>86</sup> The contribution by informants (relatives and nurses) to the diagnosis of delirium is clearly helpful and some assessment tools have this capacity, though it may become difficult to standardize as quality and quantity of informant information may vary. More specific recommendations regarding assessment tools are made separately in this section.<sup>45</sup>

Any multicenter study will require careful monitoring and a quality assurance program to optimize interrater reliability.<sup>83</sup> Ongoing

support throughout the study is necessary, though some of this could be Web or teleconference based. In-person training is also essential, involving supervised assessments at regular intervals throughout the study.

The same issues for case ascertainment are relevant to the measurement and standard definition of predisposing and precipitating factors, albeit with less impact on statistical power. Although predisposing and precipitating factors may converge in the terminal trajectory, pre-existing cognitive impairment is such a strong risk factor for delirium that this key variable must be incorporated in the initial clinical assessment. Again, the issue of trade-off between burden and comprehensiveness from a psychometric perspective arises in relation to a baseline measure of cognitive function. The choice of what biomarker(s) to evaluate as a predictor of delirium risk or reversibility is a controversial one. Based on its demonstrated prognostic potential as an index of inflammation in patients with advanced cancer, C-reactive protein should be considered in this regard.<sup>87</sup>

*Longitudinal Assessments in Delirium.* Serial measurements are essential in delirium because of its fluctuating nature and serve to improve case ascertainment. It is also particularly important to generate data toward a predictor model of reversibility. Longitudinal analyses are more powerful as intraindividual change (over time) can be separately modeled from interindividual change (performance in relation to the rest of the group). However, the observational nature of longitudinal delirium studies precludes drawing a direct cause-effect conclusion. One of the biggest challenges with longitudinal assessments in the palliative care population is attrition, due to either death or subjects' inability to participate in assessments as their disease advances. To properly account for the fluctuating nature of the syndrome, variable length of each episode, time between episodes, missing data, censored follow-up, and repeated measures of changing patient characteristics over the course of care, appropriate statistical analytical plans are a necessity. Longitudinal statistical approaches have been comprehensively reviewed by Adamis.<sup>88</sup> While the analytical framework should be tied to the particular needs of the research objectives, special

consideration should be given to flexible methods, such as generalized estimating equations and mixed-effects models, for predictor and risk factor evaluation. Moreover, if time is under investigation, special models of survival analysis such as recurrent events analysis can be used. In general, longitudinal data are richer and more informative and they can be easily analyzed with modern software.

#### *Next Steps in the SUNDIPS-Initiated Program of Research*

We are currently conducting a formal scoping review of the literature on delirium in palliative care settings, aiming to broadly provide a literature map of study designs, and thereby further highlight evidence gaps. For many of the individual questions in the analytical framework, we plan to conduct systematic reviews. Although the initial SUNDIPS meeting generated a broad collaborative commitment, the specifics of further collaboration in initial pilot and feasibility studies will need to be addressed. These include agreed commonality of study eligibility criteria, assessment tools, diagnostic criteria, outcome measures, and the pursuit of funding opportunities. In addition, we acknowledge the potential for selection bias in our small pilot survey of the SUNDIPS meeting participants. Accordingly, we are planning to expand the survey to palliative care specialists at an international level, aiming to assign a priority level to the research questions and identify any additional areas of clinical equipoise and perceived barriers to multicenter observational or interventional study participation. The support of relevant organizations such as the American Academy of Hospice and Palliative Medicine, National Hospice and Palliative Care Organization, American Delirium Society, European Delirium Association and European Association for Palliative Care, the Palliative Care Clinical Studies Collaborative in Australia, and All-Ireland Institute of Hospice and Palliative Care will be sought to promote research collaboration, knowledge translation initiatives, and ultimately guideline and policy development.

#### *Conclusions*

Delirium in palliative care settings is characterized by some remarkable clinical vagaries;

not least its reversibility, even in advanced illness; yet predicting the outcome of an episode of delirium is often difficult. Delirium is associated with personal and family distress, poorer patient outcomes, health-care professional challenges, and greater health-care costs. The projected demographic shift toward an aging population will contribute to an increased number of patients with dementia, cancer-related deaths, and a high level of comorbidity, making a compelling argument to conduct further high-quality studies of delirium in palliative care settings. Using an analytical framework to represent the clinical pathway of delirium in palliative care, we developed a series of research questions, broadly addressing epidemiology, including risk factor evaluation; screening; diagnosis; pragmatic management issues (pharmacologic and non-pharmacologic); and development of predictive models for delirium outcomes. Given recruitment and attrition challenges in this population, multicenter collaboration will likely be a key solution. Ultimately, the knowledge generated from better epidemiologic and therapeutic interventional data will inform decision making and policy development for delirium detection and management and thus help to achieve better outcomes for patients in palliative care settings.

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