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A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank

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Abstract

Delirium is an acute disorder of attention and cognition. It occurs across the life span, yet it is particularly common among older adults, and is closely linked with underlying neurocognitive disorders. Evidence is mounting that intervening on delirium may represent an important opportunity for delaying the onset or progression of dementia. To accelerate the current understanding of delirium, the Network for Investigation of Delirium: Unifying Scientists (NIDUS) held a conference "Advancing Delirium Research: A Scientific Think Tank" in June 2019. This White Paper encompasses the major knowledge and research gaps identified at the conference: advancing delirium definition and measurement, understanding delirium pathophysiology, and prevention and treatment of delirium. A roadmap of research priorities is proposed to advance the field in a systematic, interdisciplinary, and coordinated fashion. A call is made for an international

consortium and biobank targeted to delirium, as well as a public health campaign to advance the field.

KEYWORDS
biomarkers, definition, delirium, dementia, diagnosis, measurement, pathophysiology, prevention, public health campaign, treatment

1 | INTRODUCTION

Delirium, an acute disorder of attention and cognition, is a common, serious, and potentially preventable clinical syndrome in older persons. Commonly occurring after acute illness, surgery, or hospitalization, the development of delirium often initiates a cascade of events culminating in loss of independence, increased morbidity and mortality, and high health-care costs. Moreover, delirium has been associated with long-term cognitive decline, including incident dementia.[1–3] In the United States, five older persons develop delirium each minute annually, 2.6 million older adults are affected, costing the health-care system >$164 billion.[4] Given its adverse impact on functioning and quality of life, delirium holds tremendous societal implications for the individual, family, community, and health-care systems.

In recognition of the importance of delirium, the National Institute on Aging (NIA) issued a request for applications to create collaborative networks to advance delirium research in 2016. In response, the Network for Investigation of Delirium: Unifying Scientists (NIDUS) was created with the overarching goal of developing a collaborative network to advance scientific research on the causes, mechanisms, outcomes, diagnosis, prevention, and treatment of delirium in older adults. The network spans more than 27 institutions with an interdisciplinary consortium of investigators dedicated to delirium research, who work together to advance the field in an integrated and collaborative fashion. NIDUS provides research resources and training programs to enhance these efforts (https://deliriumnetwork.org).

Despite the potentially modifiable burden of delirium on our public health system, existing gaps in knowledge continue to limit fundamental new advances in prevention and treatment of delirium. Thus, NIDUS, with support from the NIA, held a Scientific Think Tank on June 16, 2019. The goal of the Scientific Think Tank was to identify major knowledge gaps in delirium research and to propose a roadmap with priorities for future delirium research. This report highlights the discussion and key priorities for the field of delirium, which spanned the areas of delirium definition and measurement, pathophysiology, and prevention and treatment.

2 | ADVANCING DELIRIUM DEFINITION AND MEASUREMENT

First and foremost, the field cannot advance without an accepted, uniform, operationalized definition of delirium, and standardized approaches to its measurement. The Scientific Think Tank participants identified the following priority areas to advance the definition and measurement of delirium: (1) consensus on the definition of delirium; (2) development of a reference standard approach for the diagnosis of delirium; (3) use of uniform, standardized measurement tools for delirium case identification and severity rating across different care settings; (4) identification of etiologic subtypes of delirium; and (5) development and application of a core outcomes set (COS) for clinical studies in delirium.

2.1 | Refinement of the definition of delirium

The construct of delirium is complex. While inattention is the core feature, considerable variability exists surrounding the presence and degree of other symptom domains, such as altered level of arousal, global cognitive dysfunction, and psychotic features. Currently, there is no definitive diagnostic test for delirium; hence, detection of delirium must rely on eliciting the key clinical features using a combination of patient interview, cognitive testing, observation, and informant history. However, the component features of delirium lack explicit and accepted definitions, and there is little consensus on operationalization and assessment methods of the individual symptom domains. Reconceptualizing delirium would require expert panel approaches, ideally combining clinical and psychometric approaches, to identify and rank key domains and supporting features. Until such consensus can be achieved, application of a smaller set of harmonized delirium measures would help to speed advances in the field.

2.2 | Use of uniform, standardized measurement tools for measuring delirium, and its severity

There is a marked variation in how the features of delirium are assessed in both clinical practice and research, ranging from subjective clinical judgment to comprehensive methods supported by cognitive testing.[5] Currently, more than 40 delirium instruments are in active use; often rating different clinical features of delirium. Thus, our ability to compare or combine results across studies using these disparate instruments is severely impaired. To address this gap, we recommend more rigorous development and validation of delirium instruments, particularly those focused on operationalizing the reconceptualized definition

of delirium. This should involve explicit descriptions of the constructs and domains, along with the use of quantitative, objective instruments that are well validated using formal psychometric approaches (ie, reliability, validity, discriminatory power, and normative data). At the same time, these new approaches need to consider the challenges of delirium assessment in real-world practice. This, in turn, will inform the development of more reliable, robust, and standardized assessments of delirium presence and delirium severity.[6] The NIDUS Measurement Harmonization Core provides detailed information cards on delirium instruments, and tools to harmonize existing measures (https://deliriumnetwork.org/measurement).

2.3 | Development of a reference standard for diagnosis of delirium

The uncertainty concerning the conceptualization and measurement of delirium has had important implications for the delirium reference standard used in research, because there is no common reference standard for delirium that is uniformly applied across studies at this time.[5] We recommend detailed and explicit documentation of the reference standard assessment process in all studies, including specification of the methods used to assess the individual features of delirium. A collaborative approach toward developing and refining a common reference standard, incorporating agreed-upon assessment methods, and a robust diagnostic algorithm is critical to advance delirium research. Such an approach will increase the consistency of case ascertainment and improve the generalizability and comparability of research findings across studies.[7,8]

2.4 | Identification of etiologic subtypes of delirium

Current measures capture different phenomenological subtypes (eg, hyperactive, hypoactive, subsyndromal), but do not capture the heterogeneity of the underlying etiology. The ability to distinguish the etiologic subtypes of delirium will be critical to develop more effective and targeted delirium interventions; an approach that is similar to pathophysiologically targeted advances in other fields such as cancer and heart disease. Future assessment of delirium should incorporate standardized strategies to evaluate for the presence of important physical examination and laboratory findings, and assessment of other potential contributors (delirium risk factors such as medications, dehydration, metabolic derangements, infections, organ failure, and underlying dementia), comorbid diseases, and detailed substance use histories. Due to the fact that delirium is typically of multifactorial etiology, the development of rigorous approaches to identify the main cause(s) of delirium will be helpful. Biomarkers, including electrophysiologic, fluid (cerebrospinal, blood), and neuroimaging, may contribute to better etiologic discrimination in the future. Although such additional approaches may prove too time consuming and expensive for standard clinical practice, it will be important to adopt detailed biomarker analysis of different etiologic subtypes in clinical research settings to elucidate the underlying pathophysiology and to develop effective treatments for delirium.

2.5 | Application of a core outcomes set for clinical studies in delirium

Another key measurement issue for delirium investigation is consistent adoption of a standardized approach to measuring delirium-related outcomes relevant to delirium research. This issue is important to advance clinical trials, and prognostic and pathophysiologic studies of delirium. A COS represents a minimum set of outcomes (ie "what" to measure) that all trials in a specific field should always measure. A COS may be accompanied by recommendations for specific measurement instrument(s) to be used for each outcome (ie, "how" to measure). This approach has been applied to many clinical conditions and treatment approaches to promote consistency and comparability across clinical trials, to improve clinical decision making, and to improve efficiency and generalizability of research findings.[9-13] A COS is typically developed through rigorous generation of outcomes/measures (eg, via systematic review and expert input) and consensus techniques (eg, modified Delphi method) with engagement of key stakeholders, such as patients, caregivers, clinicians, researchers, regulators, research funders, and industry representatives. An international effort is under way to develop delirium COS, the Del-COrS study[14] in four patient groups: (1) critical care, (2) acute hospitalization without critical care admission, (3) palliative care, and (4) older adults in long-term care or living in the community. Once developed, this COS will provide an important resource to advance clinical research in delirium.

3 | ACCELERATING UNDERSTANDING OF DELIRIUM PATHOPHYSIOLOGY

The pathophysiology of delirium remains unclear; yet an understanding of this is essential for developing pathophysiologically targeted treatments essential for precision medicine. The Scientific Think Tank recognized that elucidating the pathophysiology of delirium will benefit from both development of laboratory animal models, as well as human fluid (blood, cerebrospinal), neuroimaging, and neurophysiological biomarker studies. As each of these assessment methods provides only partial insights into the complex biology of delirium, transdisciplinary approaches that synthesize data from multiple approaches provide an opportunity for a broader understanding of delirium.

3.1 | Laboratory animal models of delirium

Laboratory models are required to evaluate potential mechanisms of delirium-like behavior in vulnerable animals in an experimental

setting, an approach that would not be feasible or ethical in humans. To enhance usefulness, animal models should be expected to meet criteria for construct validity (ie, precipitated by etiological factors known to contribute to delirium) and face validity (eg, observing cognitive and behavioral changes seen in human delirium). Specifically, these models should closely approximate the accepted criteria for delirium: (1) presence of acute and transient cognitive changes not better explained by an underlying neuropathological condition;[15] (2) ideally, demonstration of a fluctuating course;[16] and (3) instigation by acute physiologic stimuli, such as surgery, inflammation, infection, hypoxia, medication(s), or hypoglycemia. Relevant animal models should not be held to higher standards than those for other complex and heterogeneous neurological disorders such as mouse models of dementia, schizophrenia, or autism, which are widely used despite not representing these full clinical syndromes. What is essential is that delirium features are reproducibly demonstrable in blinded, randomized, and appropriately powered experiments. Cross-validation of these behavioral changes with human neurophysiological measures (eg electroencephalogram [EEG] changes),[17,18] may provide further model validation, and may provide insights into underlying pathophysiologic mechanisms.

Several animal models have been developed and while demonstrating some features of delirium in the setting of sepsis,[19] surgery,[20] and delirium superimposed on dementia,[21] all would benefit from further validation. These models have proven useful in providing a conceptual framework for how peripheral changes in inflammation, blood-brain barrier permeability,[22] and metabolism can bring about acute cognitive changes.[23] However, to reach their potential, considerable work is required to define the cellular and molecular pathways that lead to acute neuronal dysfunction, and determine how neuronal dysfunction leads to alterations in brain networks and behavior. Delirium may arise by different mechanisms across different clinical settings, and each setting may require different model systems, although some commonalities in mechanisms are likely. Shared behavioral endpoints, for example focusing on attention processing, should also be adopted and standardized across laboratories to provide targeted information about selected cognitive domains of relevance to delirium. With the further development and refinement of these model systems, we anticipate significant future progress in elucidating mechanisms of neuroinflammation and neurotransmitter modulation on brain dysfunction. Exploring the roles of altered neurovascular coupling and disrupted brain energy metabolism in delirium are also priority areas. Ultimately, these mechanistic studies hold great promise to identify key targets for interventions in future delirium clinicaltrials.

3.2 | Fluid (blood, cerebrospinal) and neurophysiological biomarkers of delirium in humans

In addition to laboratory animal models, biomarkers may provide insights into the molecular mechanisms and systems biology underlying delirium and its associated complications in humans. Although there are increasing numbers of studies collecting biospecimens from patients, these studies vary in sample size, clinical settings (eg, peri-operative, intensive care unit), types of samples collected (eg, blood, cerebrospinal fluid, urine) and specimen processing methods. As a result, it has been difficult to identify biomarkers that are consistently associated with delirium.[24,25] In addition, new delirium biomarkers may emerge from neuroimaging (eg, structural or functional magnetic resonance imaging [MRI]) or neurophysiology (eg, resting-state, intra-operative, or sleep EEG). Recent studies demonstrate patients with postoperative delirium exhibit neurophysiological patterns detectable by modern signal processing and machine learning methods.[26] Future research would benefit from standardized approaches to specimen collection, analyses, data reporting, imaging sequences, and biomarker assessment.

3.3 | International Delirium Biomarker Consortia and Biobanks

One of the proposed ways to further stimulate biomarker research is through an international biomarker consortium. Such an effort has the potential to build large-scale data and specimen banks to conduct systems biology, -omics (eg, proteomics, metabolomics), and machine learning studies to accelerate the advancement of scientific knowledge in the field. Similar consortia and biobanks already exist for a number of other conditions and diseases; this approach is advocated in the National Institutes of Health (NIH) Open Science initiative (https://www.nlm.nih.gov/NIHbmic/nih_data_sharing_repositories.html). Many consortia already exist for dementia, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI),[27] the Mark Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID) Biomarker Development and Validation Consortium for Small Vessel Disease,[28] the Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M^2OVE AD),[29] the Dementia with Lewy Bodies (DLB) Research Consortium, and the Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) consortium.[30] The purpose of these consortia is to facilitate assembly of large patient samples (with data and specimens) for future studies. Following these examples, an international delirium consortium will enable systematic collection of clinical, biomarker, electrophysiologic, and neuroimaging data; standardization and harmonization of variables and approaches; and more detailed investigation of delirium pathophysiology, thus paving the way for precision-based approaches to prevent and treat delirium.

NIDUS provides important resources to facilitate the development of these consortia and biobanks. The NIDUS Research Hub (https://deliriumnetwork.org/delirium-research-hub) provides a detailed, indexed listing of >200 delirium studies in an effort to catalyze collaborative studies, data synthesis and meta-analyses, systematic reviews, and secondary analyses.

4 | PREVENTION AND TREATMENT OF DELIRIUM

4.1 | Multicomponent, sequential approaches

Given the complex, heterogeneous, and multifactorial causation of delirium, it is not surprising that single drug or non-pharmacologic intervention strategies have not demonstrated effectiveness for delirium prevention or treatment. In terms of what is known already, multicomponent, non-pharmacologic strategies, such as the Hospital Elder Life Program (HELP, hospitalelderlifeprogram.org) or the ICU Liberation ABCDEF bundle have demonstrated at least partial effectiveness, with >50% reduction in delirium across multiple studies.[31-33] These strategies should be further evaluated to determine minimum elements, doses required, and optimal implementation strategies. Novel approaches worth evaluating include new non-pharmacologic strategies, with recent examples including prehabilitation prior to elective surgery and use of decision-support technology to facilitate management. In terms of pharmacologic approaches, further evaluation of intriguing drugs should be advanced, including dexmedetomedine,[34] caffeine, acetaminophen, melatonin and agonists, and other sleep enhancement approaches.

Future treatment targets will arise out of pathophysiological research, and it is likely that treatments will need to be multicomponent. An evidence-based, multicomponent bundle that encompasses both non-pharmacological and pharmacological interventions targeted to proven risk factors and pathophysiologic pathways should be considered. Consideration of sequential approaches, targeting multiple biologic targets on delirium pathways, might prove a more effective approach than treatments aimed at a single target.

4.2 | Novel trial designs

The traditional randomized controlled trial (RCT) is not well suited to addressing multiple interventions in heterogeneous populations who may have different outcomes and responses to therapeutic interventions. Recent innovations in clinical trial design help to overcome limitations of the traditional RCT. Bayesian or adaptive trials allow continual design modifications while the trial is ongoing, allowing customization to multiple subpopulations and interventions.[35] This approach allows for prespecified modifications to key aspects of the trial as information regarding patient characteristics and outcomes accumulate, and areas of uncertainty regarding the true efficacy of the interventions being studied are reduced. Aspects that can be modified include sample size, randomization ratio, number of treatment groups, treatment administered or treatment dose, and the patient subpopulation being considered (allowing selective recruitment of populations most likely to benefit).[35] Platform trials are a type of adaptive design that may be of particular utility in delirium research as they evaluate multiple treatments simultaneously, based on the assumption that populations of patients with disease are heterogeneous and may respond differently to the same intervention.[36]

Complementary to individualized precision medicine are more broad-based approaches to delirium prevention and treatment. RCTs examining efficacy—including adaptive designs—are useful to evaluate the treatment effect of interventions applied to selected populations under controlled conditions. By contrast, pragmatic RCTs assess the clinical effectiveness of interventions applied broadly in routine clinical care, and are useful to establish evidence-based guidelines and practice standards.[37,38] The most appropriate way to evaluate these broad approaches to care, such as clinical algorithms or hospital-wide delirium prevention and management pathways, is to assess their impact on a population under the same conditions as in actual practice.[38] Historically, researchers have done this by randomizing interventions at the level of a patient grouping (or cluster), rather than at the level of the individual patient. Most often, in delirium research, patients are clustered at the level of a hospital, ward, intensive care unit (ICU), or other clinical setting. Other randomized pragmatic designs are nested in cohort studies or registries, such that patient data and outcomes are collected from trial and administrative databases, rather than collected by research staff.[39] The advantages of this approach are that the cohort provides a pool from which patients can be recruited, multiple interventions can be tested simultaneously, and control arm outcomes are available.[39] Similarly, registry-based randomized trials use clinical databases (ie, administrative datasets retained by hospitals, clinical trials networks, health-care systems, etc) as a platform for case records, data collection, randomization, and follow-up, resulting in improved efficiency and cost. The limitations of registry-based randomized trials include concerns about the quality of the registry data due to lack of blinding, standardized patient management procedures, and standardized outcomes assessments.[40] To develop new treatments for delirium, researchers hope to target pathophysiologic mechanisms to treat specific etiologic phenotypes of delirium. Testing these customized interventions requires modifications to traditional clinical trial designs, which may be accomplished using adaptive or Bayesian designs. However, beyond individual patients, there remains limited evidence about what constitutes best practice at the institutional level. To guide broad-based practice, large pragmatic trials are required to establish the clinical effectiveness of system-wide measures focused on delirium prevention and treatment.

5 | INCREASING DELIRIUM AWARENESS AND FUNDING

Delirium is now increasingly recognized as a public health priority, an often-preventable condition ready for quality improvement efforts across clinical settings. Delirium has emerged as a focus of prevention for the Age Friendly Hospitals Initiative by the Institute of Healthcare Improvement.[41] The American Association of Retired Persons is developing public education materials about delirium as part of its Global Brain Health Initiative. The National Quality Forum has developed delirium quality measures for hospitals. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* has recognized delirium as an important and unexplored opportunity for dementia prevention, and

TABLE 1 A roadmap for advancing delirium research: Proposal from the NIDUS Scientific Think Tank

Domain	Priority areas	Description
Definition and measurement	Refining the construct of delirium	• Consensus approaches to identify key domains and supporting features of delirium • Widespread and consistent application of new operationalized definition
	Uniform measurement tools for delirium identification and severity	• Small set of standardized, well-validated instruments for delirium • Short- and long-forms for clinical and research application • Consistent usage
	Reference standard for diagnosis of delirium	• Consensus approach to develop common reference standard definition and assessment • Robust diagnostic algorithm • Consistent application
	Etiologic subtypes of delirium	• Standardized approaches to identify underlying contributors to delirium • Incorporate biomarkers • Use subtyping to target treatment
	Core outcomes set for delirium studies	• Specified outcomes for clinical trials and studies of delirium • Tailored to specific clinical settings • Consistent application
Pathophysiology	Laboratory animal models for delirium	• Experimental induced delirium in vulnerable animal • Meet construct validity (accepted precipitating factor) and face validity (manifests some delirium domains) • Test hypothesized pathophysiologic mechanisms to identify targets for future treatment trials
	Biomarkers for delirium in humans	• Standardized approaches for specimen collection, analyses, and reporting • Novel biomarkers: fluid, neuroimaging, electrophysiologic • Discovery may involve advanced approaches, including signal processing and machine learning
	International consortia and biobanks	• Large-scale data and specimen banks to facilitate systems biology, -omics (eg, proteomics, metabolomics), and machine learning studies • Systematic collection of clinical, biomarker, electrophysiologic, neuroimaging data, along with harmonization of variables and approaches
Prevention and treatment	Multifactorial, sequential approaches	• Novel approaches to prevention • Multicomponent treatment bundle, including nonpharmacologic and pharmacologic interventions targeted to proven risk factors and pathophysiologic pathways • Sequential treatment approaches, targeting multiple biologic targets on pathways
	Novel trial designs	• Adaptive trial designs (eg, Bayesian, platform) that allow customization while trial ongoing to refine interventions and study subpopulation • Pragmatic trials to evaluate system-wide or large-scale management strategies • Registry-based clinical trials to improve efficiency and reduce costs
Public health campaign	Educational and public health campaigns	• Public education to increase awareness, improve research funding, and address ageism and the stigma of delirium and dementia • Workforce development and training of health-care professionals • Larges-cale implementation of effective approaches for prevention and management of delirium • Follow Alzheimer's disease approach • Define societal impact and economic costs of delirium • Health policy efforts to advance delirium awareness, prevention and clinical care, and research

has established a special topic section to raise the visibility of delirium in the Alzheimer's disease (AD) research community. There is a strong international consensus about the need for a grassroots effort to improve the public's awareness of, and increase funding for, delirium using a similar public health campaign model that has driven AD prevention into the international forefront of health policy planning. The International Drive to Illuminate Delirium (IDID) seeks to advance the field of delirium along five pillars: awareness, policy, diagnosis, burden, and biology. This campaign will draw upon the same methods and procedures used to increase public awareness and research funding for AD. The initial core functions for the campaign include the assembly of international experts, from multiple disciplines, participating in work groups to develop plans that will lessen the burden due to delirium over the next 10 years. This campaign seeks to produce a series of consensus and implementation documents that will identify key challenges, potential demonstration projects, research priorities, and cost estimates to help reduce the burden of dementia due to delirium.

6 | A ROADMAP FOR DELIRIUM RESEARCH

Based on the discussion at the NIDUS Scientific Think Tank, Table 1 provides a potential roadmap of research priorities to advance the field. This represents a compilation of the important gaps in knowledge needed to move the delirium field forward. Systematic and thorough investigation of the issues and questions identified here will lay the groundwork for fundamental advances in delirium research and clinical practice. We hope this roadmap will provide a call to action for the field and catalyze continued advances in this important and neglected area.

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