Title: Tackling Brain and Muscle Dysfunction in Acute Respiratory Distress Syndrome Survivors: National Heart, Lung, and Blood Institute Workshop Report

Authors:

Jessica A. Palakshappa, MD MS*[1]; Jane A. E. Batt, MD PhD[2]; Sue C. Bodine, PhD[3]; Bronwen A. Connolly PhD, MCSP[4]; Jason Doles PhD[5]; Jason R. Falvey PT, DPT, PhD[6]; Lauren E. Ferrante MD, MHS[7]; D. Clark Files MD[1]; Michael O. Harhay PhD, MPH[8]; Kirsten Harrell, PsyD; Joseph A. Hippensteel, MD, MS[9]; Theodore J. Iwashyna MD, PhD[10]; James C. Jackson PsyD[11]; Meghan B. Lane-Fall MD, MSHP[8]; Michelle Monje MD, PhD[12]; Marc Moss MD[9]; Dale M. Needham MD, PhD[10]; Matthew W. Semler MD, MSCI[11]; Shouri Lahiri MD[13]; Lars Larsson MD, PhD[14]; Carla M. Sevin MD[11]; Tarek Sharshar PhD[15]; Benjamin Singer MD, PhD[16]; Troy Stevens PhD[17]; Stephanie P. Taylor MD[16]; Christian R. Gomez PhD[18]; Guofei Zhou PhD[18]; Timothy D. Girard, MD, MSCI*[19]; Catherine L. Hough, MD, MSc*[20]

[1]Wake Forest University School of Medicine

[2]University of Toronto Temerty Faculty of Medicine

[2]Oklahoma Medical Research Foundation and Oklahoma City Veterans Affairs Medical Center

[4]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK

[5]Indiana University School of Medicine

[6]University of Maryland School of Medicine

[7]Yale University School of Medicine

[8]University of Pennsylvania Perelman School of Medicine

[9]University of Colorado School of Medicine

[10]Johns Hopkins University School of Medicine

[11]Vanderbilt University School of Medicine

[12]Howard Hughes Medical Institute, Stanford University

[13]Cedars Sinai Medical Center

[14]Center for Molecular Medicine, Karolinska Institute, Sweden

[15]Neuro- Intensive Care Medicine, GHU-Psychiatrie & Neurosciences, Sainte-Anne Hospital, Université Paris Cité, Paris, France

[16]University of Michigan

[17]University of South Alabama

[18]Division of Lung Diseases, NHLBI

[19]Center for Research, Investigation, and Systems Modeling of Acute illness (CRISMA) in the Department of Critical Care Medicine; University of Pittsburgh School of Medicine; Pittsburgh, PA, USA

[20]Oregon Health & Science University

Corresponding Authors:

Jessica A. Palakshappa, MD MS*

2 Watlington Hall

1 Medical Center Boulevard

Winston-Salem, NC 27157

Email: jpalaksh@wakehealth.eud

Timothy D. Girard, MD, MSCI*

Catherine L. Hough, MD, MSc*

*****These authors have equally contributed to this manuscript and are co-corresponding authors.

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Abstract

Acute respiratory distress syndrome (ARDS) is associated with long-term impairments in brain and muscle function that significantly impact the quality of life of those who survive the acute illness. The mechanisms underlying these impairments are not yet well understood, and evidence-based interventions to minimize the burden on patients remain unproven. The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health assembled a workshop in April 2023 to review the state of the science regarding ARDS-associated brain and muscle dysfunction, to identify gaps in current knowledge, and to determine priorities for future investigation. The workshop included presentations by scientific leaders across the translational science spectrum and was open to the public as well as the scientific community. This report describes the themes discussed at the workshop as well as recommendations to advance the field toward the goal of improving the health and wellbeing of ARDS survivors.

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Introduction

Acute respiratory distress syndrome (ARDS) is a common, heterogeneous critical illness syndrome resulting in lung injury, respiratory failure, and, frequently, death. Prior to the COVID-19 pandemic, approximately 190,000 people developed ARDS in the United States each year with an estimated 5-fold increase in the incidence of ARDS during the pandemic (1, 2). While short-term mortality from ARDS remains unacceptably high at over 40%, case fatality has declined in recent decades resulting in a growing population of ARDS survivors (3-5). These survivors often experience long-term or permanent sequelae of brain and muscle dysfunction that significantly impact their quality of life and ability to function within their community (6). For more than two decades, clinicians and researchers have recognized that brain and muscle dysfunction persist for months to years after ARDS (7, 8). Though our understanding of the clinical presentation of these impairments and many of the individual risk factors impacting their development has deepened, evidence-based approaches to prevent brain and muscle dysfunction in ARDS patients as well as intervention targets designed to improve existing impairments in this population remain elusive.

To examine the state of science, address knowledge gaps, and propose future directions to decrease brain and muscle dysfunction following ARDS, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health assembled a workshop in April 2023. The workshop was open to members of the scientific community and the general public. The two-day virtual meeting included scientific presentations by leaders of research spanning the translational science spectrum from pre-clinical research to implementation science and a small group discussion focused

on addressing gaps in mechanistic and clinical studies of brain and muscle dysfunction following ARDS. During scientific presentations and small group discussion sessions, we collected notes and used these notes to generate this report, which summarizes the workshop's scientific presentations and the themes discussed throughout the workshop. The primary writer, who was identified prior to the workshop, participated in planning the meeting and—along with the co-chairs, scientific presenters, a patient representative, and two members of the NHLBI—contributed to the report and agreed on the content presented.

Herein, we summarize the state of the science presented during the individual scientific presentations as well as the knowledge gaps identified during discussion. We have organized the report to follow the themes and structure of the workshop, which were determined during planning meetings held by the primary writer, the co-chairs, and NHLBI representatives. We have also included recommendations reviewed by all workshop participants for advancing the science of this field.

Develop Rigorous and Personalized Measurements of Brain and Muscle Dysfunction in ARDS Survivors

Persistent functional and cognitive impairments following ARDS have been described in observational cohort studies as well as systematic post-hospital follow-up after randomized clinical trials of ARDS interventions (7, 9-11). The reported prevalence of post-ARDS complications has varied depending on the population studied, instruments used to measure impairments, and the timing of the assessments (12-14). Impairments have been reported across multiple domains including, but not limited to,

muscle weakness, mobility limitations, cognitive impairment, mental health symptoms, and a worsening of chronic health conditions(6, 14) (**Figure 1**). This constellation of symptoms and impairments is often referred to collectively as “post-intensive care syndrome (PICS)” (15). At present, there are no formal diagnostic criteria for this syndrome and many key knowledge gaps in measuring and describing these impairments still exist. Both brain and muscle dysfunction are significant contributors to PICS and the focus of this workshop report.

Brain dysfunction following ARDS has been most often described as new or worsening cognitive impairment following critical illness, though no formal diagnostic criteria for ARDS-related brain dysfunction exist. In a three-round modified Delphi consensus process designed to develop a Core Measurement Set for clinical research studies of acute respiratory failure survivors, no measure for cognition reached the threshold for consensus (16). In most prior studies of ARDS survivors, cognitive impairment was measured using validated cognitive assessments (such as the Montreal Cognitive Assessment test (17) which is recommended in the Core Measurement Set for clinical research studied), which are often referenced to population norms and adjusted according to key factors such as age, sex, and level of education. Since cognitive assessments often involve multiple tests, impairment is often defined as scoring ≥1.5 standard deviations (SDs) below the population mean on ≥2 tests or ≥2 SDs below the mean on at least one test. The limitation of this approach is that performance on a cognitive assessment tool does not necessarily reflect the ability to function in the “real world.” Patients and their families are interested in understanding and improving their ability to accomplish real-world tasks such as resuming domestic

roles and returning to full-time employment, studies, or other vocations (18). Research on aging has recently emphasized understanding cognition by evaluating how older adults solve problems encountered in daily life (19). This concept has not yet been applied to post-ARDS cognitive impairment. Future work is needed to understand the ecological validity of cognitive performance measures in ARDS survivors.

Muscle dysfunction following ARDS has been defined using both volitional strength (e.g., manual muscle testing) and structural (e.g., muscle ultrasound and muscle biopsy) assessments (20, 21). The term intensive care unit-acquired weakness (ICUAW) has been used to describe symmetric, diffuse weakness of the limb and respiratory muscles for which no other plausible etiology other than critical illness has been identified. A total score of less than 48 out of 60 determined by manually testing the muscle strength using the Medical Research Council scale supports a diagnosis of ICUAW (22, 23). Handgrip dynamometry has also been used as diagnostic test for ICUAW. Changes in cross-sectional area of the quadriceps muscle and muscle echointensity on ultrasound have also been used to describe changes in muscle architecture, though there are no widely established definitions using these modalities (24). Finally, cross-sectional area and ratio of protein to DNA has also been determined histologically on limb muscle biopsy samples to describe skeletal muscle dysfunction in ARDS (20).

While these different assessments each provide useful and complimentary information on the degree of different aspects of muscle impairment during and after ARDS, their relationship to each other is not well understood and may have limited correlation due to the individual nature of each testing approach. Volitional strength

assessment necessitates patients have adequate cognitive and executive ability to follow test instructions, coordination to perform test maneuvers appropriately according to each muscle group, and motivation to perform to their maximum capacity. These factors mean that a patient may score poorly on manual muscle strength testing suggesting muscle weakness, but structural correlates may not be reflected in non-volitional measures, such as muscle architecture (e.g., cross-sectional area visible on ultrasound), where findings are independent of patient influence. All measurements of muscle strength are also limited by variability in operator skill and psychometric properties such as floor and ceiling effects, as well as practical (e.g., which muscle or muscles to test, dominant versus non-dominant body side) and logistical (e.g., need for expensive equipment, training requirements for personnel) aspects. More research is needed to understand the interdependent nature of skeletal muscle function and overall physical function of an individual patient. As with cognitive function, patients tend to prioritize physical function over isolated muscle strength; they value function that facilitates real-world tasks, which has typically not been measured in prior studies. There is also a need to define what aspects of muscle strength and function can be measured serially across the continuum of care settings for patients recovering from ARDS.

Social determinants of health (SDOH) are defined as the conditions in the environment where people are born, live, learn, work, play, and age that impact a wide range of health and quality-of-life outcomes including recovery from critical illness and ARDS (25). While the need to identify and address SDOH to improve the management of chronic health conditions has been increasingly recognized, the impact of SDOH on

critical illness recovery has only been more recently explored. Lower individual socioeconomic status, determined by dual eligibility for Medicare and Medicaid, was associated in one study with 28% greater disability burden and 9.8-fold greater odds of developing dementia after an ICU hospitalization (26). Living in a disadvantaged neighborhood, defined using the area deprivation index, and being socially isolated are also associated with an increased disability burden after an ICU stay (27, 28). Alternatively, education is associated with a protective effect; more years of education was associated with greater odds of being free of PICS at 3 and 12 months (29).

While SDOH likely impact both physical and functional outcomes, ARDS and critical illness in general may exacerbate existing inequalities. ARDS may result in inability to return to work and new or worsening financial toxicity, further worsening cognitive and physical function (30-32). Understanding how best to measure, report, and address treatment barriers related to SDOH across the continuum of ARDS recovery will be critical to advancing our understanding of persistent cognitive and functional impairments.

Finally, we need to understand how to reflect the impact of social, physical, and environmental factors and the influence of patient adaptation when understanding recovery of cognitive and physical function after ARDS (33, 34). The definitions of brain and muscle dysfunction should evolve to incorporate the evolving and adaptive preferences of patients recovering from critical illness. And, as a scientific community, we must be careful not to equate disability with poor health. This will require us to examine how structural ableism may impact patients' ability to access both clinical care and participate in research studies of persistent impairments following ARDS (35).

Advance our Understanding of Brain Dysfunction: Pathogenesis and Recovery

Cognitive impairment is common during and after ARDS. As many as 70% of ARDS patients are cognitively impaired during critical illness with delirium (36). This syndrome of acute and fluctuating brain dysfunction resolves in the hospital for almost all survivors, but many continue to have cognitive impairment after resolution of delirium. Cohort studies of survivors—most of which determined prevalence of impairment by comparing cognitive performance of subjects with age-adjusted norms—have reported a prevalence of impairment ranging from 70% to 100% at hospital discharge and 25% to 47% at one year following discharge (37). For some, cognitive deficits may resolve in the months following the acute illness, but in other ARDS survivors, a persistent cognitive impairment or acquired dementia occurs (9, 38). Though the pathophysiologic mechanisms underlying the development of persistent cognitive impairment following ARDS are not fully understood, it is increasingly clear that crosstalk exists between the lung and the brain (39, 40). Preclinical studies involving porcine models of ARDS have identified neuroinflammation, which correlated with markers of neuronal damage, as well as perivascular inflammation and direct neuronal damage in the hippocampus (41). Neuronal necrosis and apoptosis have also been demonstrated using an in vitro model of lung injury (42). Bench-bedside-bench (i.e., forward and reverse translational) studies of both acute effects of ARDS on the brain and the long-term neurologic sequelae associated with ARDS survival may offer significant insight into these mechanisms. Furthermore, translational investigations

uniting the historically siloed pre-clinical and clinical research domains are essential to inform the development and testing of mechanistically informed interventions.

Delirium has been consistently shown to be an independent risk factor for worse cognitive outcomes after an ICU stay with longer periods of delirium predicting more severe long-term cognitive impairment (9, 37, 43). The relationship between delirium and dementia is complex and bidirectional; patients with underlying dementia or a predisposition to dementia are more likely to experience delirium during acute illness, and patients with delirium are more likely to develop dementia after the resolution of their acute illness (9, 44, 45). The development of these two conditions likely involves several common pathways. It has been hypothesized that immune-mediated injury to the frontal cortex, hippocampus, and amygdala play a key role in the pathogenesis of delirium and also contribute to long-term brain dysfunction in survivors (46, 47). Both innate immune cells and soluble mediators such as complement, cytokines, and damage-associated molecular pattern molecules contribute to brain injury in systemic inflammatory states and may therefore be therapeutic targets (48-50). Systemic interleukin-6 (IL-6) inhibition, for example, has been shown to improve delirium-like behaviors in a murine model of acute lung injury and can mitigate the neuronal injury to frontal and hippocampal brain structures (51, 52). IL-6 has also been implicated in the pathogenesis of Alzheimer's Disease (AD) and may be a key link between peripheral immunologic alterations contributing to delirium during ARDS and cognitive impairment in survivors (53). These findings suggest modulation of IL-6 signaling pathways during ARDS may be a promising target for future studies of therapeutics aimed at mitigating the neurocognitive dysfunction associated with ARDS survival.

While relatively few studies have specifically evaluated the effects of lung injury on resultant brain dysfunction, host-pathogen interactions during pneumonia and lung-brain crosstalk occurring during mechanical ventilation have recently been found to potentially contribute to long-term cognitive consequences. Tau proteins, a major component of neurofibrillary tangles characteristic of AD, are expressed in pulmonary endothelial cells and can be released systemically after bacterial infection as a host defense mechanism (54, 55). Paradoxically, these tau variants can be cytotoxic and have been shown to disseminate via the circulation to the brain of patients with some forms of bacterial pneumonia. Infection-induced tau released from lung endothelium can cause neuronal tau aggregation, similar to that seen in AD, and may be an important mechanism underlying persistent cognitive impairment in ARDS survivors (54). Mechanical ventilation, and especially the use of high tidal volumes, has also been shown to result in neuroinflammation and hippocampal injury (56, 57). Even short-term mechanical ventilation increases neuroinflammatory cytokines and can promote the neuropathology of Alzheimer's disease in both wild-type mice and mice with pre-existing Alzheimer's disease cerebral pathology (52). Finally, other distinct mechanisms that have been discovered in pre-clinical models with similar implications for post-ARDS cognitive dysfunction include pathogenic endothelial glycocalyx-derived heparan sulfate molecules that disrupt neuronal function and brain-penetrating systemic myeloid cells that can initiate and propagate neuroinflammation (48, 58, 59).

Knowledge about neurocognitive syndromes in diseases and conditions distinct from ARDS may also provide important mechanistic insights into the brain dysfunction experienced by many ARDS patients and reveal unique therapeutic opportunities. For

example, the cognitive deficits seen in ARDS survivors can resemble those seen in patients with cancer-therapy-related cognitive impairment, a syndrome for which microglial reactivity and neural dysregulation are central features (60, 61). Neuroplasticity and homeostasis of white matter, important processes which underlie higher order brain functions and coordination of function among brain regions, are impacted both in chemotherapy-related cognitive impairment and in respiratory SARS-CoV-2 infection and may have a role in the brain dysfunction experienced by many ARDS survivors. The cognitive deficits experienced after ARDS also resemble those seen in patients with AD and related dementias. Given the extensive AD drug development pipeline targeting diverse mechanisms, therapeutics developed for AD may also affect ARDS-related cognitive impairment. Applying our understanding of the mechanisms involved in distinct but similar conditions will be a key step in advancing our understanding of ARDS-related brain dysfunction.

Advance our Understanding of Muscle Dysfunction: Pathogenesis and Recovery

Muscle wasting has been recognized as a common complication of ARDS and critical illness more generally, with case series and cohort studies describing the clinical presentation and prevalence of nerve and muscle injury first published over 20 years ago (22). Unpacking the pathogenesis of this muscle wasting is challenging because of the rapid kinetics and changing biological signatures occurring during ARDS. Loss of skeletal muscle mass, which is ubiquitous during ARDS, results from imbalances in cellular signaling pathways regulating protein synthesis and degradation that favor the

latter (62, 63). Stimuli affecting these processes can include systemic inflammation, hypoxia, vascular dysfunction, mitochondrial dysfunction, glucocorticoid exposure, oxidative stress and lipotoxicity, and a decrease in external loading and neural activity (62, 63). The rate and extent of muscle atrophy depends on the muscle and fiber type as well as the atrophy-inducing stressor (64). Many of these pathways likely contribute to the muscle wasting observed during ARDS, though the primary mechanisms remain unknown. While muscle atrophy is a component of the limb and diaphragmatic muscle weakness that occurs during ARDS, weakness can result from multiple etiologies including neural or neuromuscular junction injuries or pathologies that affect muscle specific force production (e.g., excitation-contraction coupling). Therefore, it is not unexpected that muscle mass and force do not uniformly correlate.

Designing interventions that prevent or improve skeletal muscle dysfunction in ARDS will require advancing our knowledge in several key areas. First, while targeting muscle proteolysis in the acute phase of ARDS is a worthy goal, it is important to appreciate that the skeletal muscle system is the largest source of proteins and amino acids in the human body, which are liberated during catabolic stress and nutrient deprivation. Classical and more recent studies in fasting humans show increases in plasma amino acids, liberated from skeletal muscle, which may fuel critical cellular processes (65, 66). Therapeutic strategies targeting the prevention of muscle proteolysis should be considered in this context, and studies are needed to quantify amino acid cycling in patients with ARDS (67). Second, recent advancements in our knowledge of the biochemical mechanisms underlying muscle atrophy have identified intracellular proteins critical to muscle wasting (such as TRIM32 or MuRF1) and others

that block atrophy (such as sirtuin1 and JUNB) (68). As our understanding deepens, these proteins may serve as therapeutic targets, through manipulation of expression levels and/or biologic activity (69, 70).

Further work is needed to understand the changes occurring in muscle not just in the acute phase of ARDS but also throughout the recovery period. This will require serial measurements of muscle function and structure; obtaining these measurements will require close collaboration between pre-clinical and clinical scientists and harmonized protocols applied across centers. It is likely that distinct interventions will be needed during different phases of illness and recovery given the dynamic kinetics of muscle injury and recovery. For example, one intervention may be most effective during the period of active muscle loss and degradation during ARDS whereas another intervention may be most effective during recovery (e.g., after ICU discharge), promoting timely and complete recovery of muscle mass via regenerative growth and force generating capacity. Second, the relationships of age and comorbid illness with the muscle dysfunction seen in ARDS are not well understood. Recovery of muscle mass and strength is impaired with aging, and it is likely that the muscles of older adults respond differently following acute illness than do the muscles of younger patients (71-73). Other conditions that are common in older ARDS patients, including chronic obstructive pulmonary disease, renal disease, and congestive heart failure are associated with impaired muscle dysfunction chronically and likely impact the muscle wasting that occurs acutely as well as its recovery (74-77).

Further work is also needed to fully understand the complex relationship between muscle strength and physical function. Physical function, including the ability to perform

basic and instrumental activities of daily living, requires the coordination of multiple organ systems in addition to adequate muscle mass and function. The impairments in physical function that many patients experience following ARDS may be related to impairments outside of or in addition to impairments in skeletal muscle, for example, impairments in balance and coordination. Designing interventions to improve physical function will require a further understanding of the mechanisms underlying skeletal muscle wasting, decreased contractility, and impaired recovery as well as when to target non-muscle contributors to functional impairment.

Move from Observations to Interventions

Brain and muscle dysfunction that may occur during and following ARDS are syndromes defined by a set of symptoms or conditions that often co-occur. Patients arrive at the syndrome of ARDS from different pathways. A 70-year-old woman with diabetes, heart disease, and chronic kidney disease who has pneumonia and ARDS, for example, is different in many ways from a 25-year-old, previously healthy man who develops ARDS in the setting of acute pancreatitis. Thus, the brain or muscle dysfunction that occurs in these two patients and their recoveries will share many features but also have important differences resulting from distinct genetics, baseline brain and muscle function, comorbid conditions, pathogens, ICU treatments, and recovery environments. The design and conduct of clinical trials evaluating interventions for brain and/or muscle dysfunction in ARDS will need to measure and account for the heterogeneity of underlying conditions and the complexities of individual patients'

recoveries. This workshop addressed several of the challenges and key knowledge gaps in advancing clinical trials in this area.

To date, most clinical trials in ARDS recovery have been explanatory randomized trials designed to evaluate the efficacy of an intervention by testing it in a tightly controlled setting. Recent critical care trials, however, have increasingly taken a more pragmatic approach, testing the effectiveness of interventions in more generalizable settings, often embedded in routine clinical care (78). These trials have primarily evaluated ICU-based interventions, and further work is needed to optimize pragmatic trials to focus on brain and muscle dysfunction after ARDS. **Table 1** lists several key areas for future work to optimize pragmatic trials supporting ARDS recovery**.** Additionally, future trials of both ICU-based and post-ICU interventions in ARDS survivors should consider studying implementation and effectiveness simultaneously in so-called “hybrid implementation-effectiveness” trials given the gap in translating interventions proven to be effective into routine clinical care (79).

Recent studies have improved our understanding of the outcomes that matter to patients and families following critical illness (16, 80-82). A core outcome set for clinical studies of ICU survivors has been created, and statistical methods for comparing functional outcomes in randomized trials have advanced (16, 83, 84). Gaps remain, however, in understanding how best to design functional outcomes that incorporate patient preferences. For example, one patient may rate the ability to walk a certain distance as very important while another patient may not find this outcome as necessary to defining his or her recovery. While outcomes that are personalized, adaptable, and function-focused may be appropriate for assessing the effectiveness of

a clinical intervention, organ-specific outcome measures are still needed to improve our understanding of how interventions effect the mechanistic changes occurring in the brain or muscle during and after ARDS. To advance translational science in this field, both patient-centered outcomes and mechanistic outcomes should be incorporated in trials when feasible. Doing so will facilitate not only the translation of preclinical findings into effective interventions but will also advance our understanding of the mechanistic basis for the clinical observations seen in the clinic or during a clinical trial, i.e., “reverse translation” (**Figure 2**).

Further work is also needed to determine the appropriate statistical analyses when evaluating the effect of an intervention on functional outcomes in ARDS survivors. In-hospital and short-term mortality remain unacceptably high in ARDS, such that interventional trials evaluating effects on functional outcomes are challenging because many participants die before such outcomes can be ascertained (83). Those who die prior to the assessment of cognition or physical function during follow-up do not have a functional outcome for analysis; their functional outcomes are “truncated due to death” (83). Functional outcomes can also be missing in survivors due to non-random factors such as persistent severe illness and institutionalization or, return to work or travel, which prevent outcome ascertainment. Several statistical techniques can be used to address this challenge, with composite endpoints being increasingly used in post-ARDS research. But such endpoints are conceptually challenging to understand and compare across studies (85). Thus, ongoing work on statistical methodology must occur simultaneously with advancements in clinical trial design.

Workshop participants discussed the future of adaptive platform trials aimed at testing multiple interventions designed to prevent or treat brain and muscle dysfunction following ARDS. A platform trial has the goal of finding the best treatment for a disease or condition “by simultaneously investigating multiple treatments, using specialized tools for allocating patients and analyzing results” (86). Given the heterogeneity of ARDS and its recovery, adaptive platform trials are appealing as a way forward to find the best treatment for particular subgroups of ARDS patients. While the adaptive platform trial design has been used to study novel therapeutics for ARDS(87), barriers exist to using this trial design to study interventions to improve ARDS-related brain and muscle dysfunction. First, and most importantly, advancements in our understanding of the mechanisms underlying these complications of ARDS are needed to develop novel interventions ready to be tested in a platform trial. Second, collaborations between scientists will need to expand to design master protocols that incorporate patient-centered and organ-specific outcomes as appropriate. Finally, platform trials require substantial resources and will need an investment that likely combines federal, foundation, and industry sources. Despite these barriers, workshop participants were optimistic about the potential of this approach and future innovation and collaboration in this field.

Conclusions

Participants of this workshop identified several key areas of focus across the translational science spectrum to further our understanding of brain and muscle

dysfunction following ARDS (**Table 2**). To accomplish this work, collaboration will be needed between preclinical scientists, clinical scientists, and biostatisticians, along with ARDS survivors and their loved ones. Further work also will be needed to embed this research into the routine care of patients; this advance will require partnerships with patients and families as well as clinicians caring for patients with ARDS from the ICU through recovery in the community. Improving our understanding of the mechanisms underlying brain and muscle dysfunction and the measurement of these complications throughout recovery will be necessary to design and test interventions that ultimately improve the care of patients.

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Figure 1 Legend: Long-Term Impairments after Acute Respiratory Distress Syndrome

Figure 2 Legend: Forward and Reverse Translation to Advance our Understanding of Brain and Muscle Dysfunction following Acute Respiratory Distress Syndrome

Table 1. Key Gaps to Improving the Design and Conduct of Pragmatic Trials for Brain and Muscle Recovery Following ARDS

Current Gap	Pragmatic Design Feature	Further Work Needed
Key patient-centered outcomes are not fully developed and often not available outside of research settings	Primary outcome is usually collected as part of routine clinical care	Embedding patient-reported outcomes and patient-generated data important to ARDS survivors into electronic health records
Lack of integration of care across multiple transitions of clinical locations and domains	Treating clinicians rather than researchers deliver trial interventions	Improve communication between clinicians treating ARDS in ICU and inpatient settings with primary care and community providers
Outcomes and patient data such as biomarkers that are important for understanding mechanism may not be easy to capture in pragmatic trials	May involve waiver of the requirement for informed consent and only use data collected as part of routine clinical care	Additional research is needed to develop an ethical and regulatory framework that respects patient autonomy while advancing needed mechanistic science
Functional outcomes may be missing given high risk of morbidity and subsequent mortality	Intention-to-treat analysis with all available data recommended	Continued advancement of statistical methods for analysis of cognitive and physical function outcomes accounting for the competing risk of death

Table 2. Recommendations for Advancing the Study of Mechanisms Underlying Brain and Muscle Dysfunction in ARDS

Domain	Recommendation
Measurement and Definition of Brain and Muscle Dysfunction in ARDS	Establish diagnostic criteria for ARDS-related brain and muscle dysfunction for use in both clinical and research domains
	Explore patient outcome measures that incorporate patient-focused functional tasks (e.g., paying a bill or bathing independently)
	Evaluate how to incorporate evolving and adaptive patient preferences when determining primary outcomes of brain and muscle dysfunction
	Develop care pathways that explicitly screen for and proactively address unmet needs related to social determinants of health to improve physical and cognitive recovery (e.g., screening for food insecurity and connecting patients with local resources)
Pathogenesis of Brain and Muscle Dysfunction	Investigate underlying pathological molecular pathways using traditional animal models of acute lung injury as well as more complex animal models that account for the heterogeneity of treatment and recovery environments
	Incorporate mechanisms known or suspected to be important in distinct-but-related syndromes of muscle and brain impairment (e.g., chemotherapy-related cognitive impairment or Alzheimer's Disease and related dementias)
	Explore approaches to manipulating the expression and/or biologic activity of proteins that promote muscle regeneration and repair during and after critical illness
Designing and Testing Interventions to Improve Brain and Muscle Dysfunction Following ARDS	Utilize forward and reverse translational studies of brain and muscle dysfunction in ARDS to develop biologically plausible interventions to be tested in clinical trials
	Establish consensus on preferred statistical methods for analyzing the effect of interventions on functional outcomes of ARDS survivors in randomized trials
	Identify patients in ARDS trials who are resilient to expected brain and muscle dysfunction and develop models of resilience through reverse translational approaches
	Use hybrid implementation-effectiveness trial designs to study clinical effectiveness while generating implementation findings needed for spread and scaling
Other	Expand access to clinical and biologic data across studies and centers