Grant Number: 5K02AG024476-02
PI Name: NELSON, JUDITH E.
PI Email: judith.nelson@mountsinai.org
PI Title:
Project Title: Improving Palliative Care in Chronic Critical Illness

Abstract: *DESCRIPTION (provided by applicant): A large and growing population of patients survives acute critical illness only to become "chronically critically ill," with profound debilitation and often permanent dependence on life-sustaining technology. Despite intensive care, outcomes for these patients remain poor: mortality rates are high and extreme functional dependence is typical for survivors. Evidence suggests substantial patient suffering during care. Chronic critical illness is a serious health problem for the nation and especially for older adults; the majority of these patients are over age 65. The Candidate for this K02 award brings expertise in critical care and palliative medicine to this important new area for aging research. Overall goals of her research program are: I. To assess palliative care needs of chronically critically ill older adults; II. To evaluate the influence of unmet palliative needs on important clinical/utilization outcomes of chronic critical illness; and III. To test targeted interventions to improve palliative care/associated outcomes of older adults with chronic critical illness. She recently received her first R01 award for research with these specific aims: 1) To assess symptom distress during chronic critical illness; and 2) To analyze associations between symptom experience and other outcomes including success in/time to liberation from mechanical ventilation, functional status and survival. Here, the Candidate presents a plan for further career development/research that will enhance the current R01 and facilitate her transition from newly independent investigator to leader of a strong, expansive, and sustainable program that continues to inform and improve palliative care for older adults with chronic critical illness. Whereas she currently carries substantial non-research responsibilities, a K02 award would protect the Candidate's time to: 1) Advance her skills/knowledge/experience in clinical research methods/project leadership, palliative medicine and geriatrics; 2) Use her ongoing observational research as a platform for successful applications for federal funding of interventional studies; and 3) Establish herself as an investigator of international stature. The environment is a renowned center for research in geriatric palliative care and chronic critical illness and for clinical research training; the institution offers enthusiastic support.*

Institution: MOUNT SINAI SCHOOL OF MEDICINE OF NYU
OF NEW YORK UNIVERSITY
NEW YORK, NY 10029
Fiscal Year: 2005
Department: MEDICINE
Project Start: 01-SEP-2004
Project End: 31-AUG-2009
ICD: NATIONAL INSTITUTE ON AGING
IRG: NIA

3. THE CANDIDATE

The Candidate, Judith Nelson, MD, JD, is currently Associate Professor in Medicine, Division of Pulmonary and Critical Care Medicine, at the Mount Sinai School of Medicine, and is a faculty member of the Hertzberg Palliative Care Institute of Mount Sinai's Brookdale Department of Geriatrics and Adult Development. Dr. Nelson has drawn on her diverse training and experience to develop an innovative research program focusing on palliative care for older adults who survive acute critical illness only to become chronically critically ill, with profound debilitation and continuing dependence on mechanical ventilation and other life-sustaining technology. Chronic critical illness is a serious national health problem of special importance for aging research: most chronically critically ill patients, whose numbers exceed 100,000, are over age 65; outcomes are poorest for these older patients; and charges, which approach $15 billion annually, are mainly attributable to care of critically ill patients aged 65 and older. In May 2003, the Candidate received her first award from the National Institutes of Health, an R01 grant from the National Institute on Aging (AG 21172-01 A2) to study symptoms and associated outcomes of chronic critical illness. She now seeks a K02 award to further her independent research program and career.

Dr. Nelson's commitment to a career in biomedical research is reflected in the professional responsibilities she has undertaken; in her assiduous, sustained, and recently successful effort to obtain research support from NIH and other sources, and in her active involvement in a variety of activities related to her pioneering research, for which she has achieved national recognition. She has been continuously engaged as a clinical investigator since 1999, as more fully described below. Whereas further development of her research program and biomedical research career requires a period of more intensive research focus, the Mount Sinai School of Medicine is placing increasing clinical, teaching, and administrative demands on Dr. Nelson and other faculty. This academic year, the institution's mandate for full salary coverage through faculty effort has entailed an increase in Dr. Nelson's non-research workload to 60% effort. The K02 award will reduce her clinical, teaching, and administrative responsibilities, allowing the Candidate to spend a minimum of 75% effort conducting research and related activities, as is needed to realize the full potential of her current R01, her overall research program, and her promising research career.

3.A. Candidate's Background

This section summarizes the Candidate's strong record of academic accomplishment, the background of her clinical research career, and her leading role in defining the field of her major research interest through theoretical and empirical contributions.

3.A.1. ***Academic Advancement***. Dr. Nelson received her A.B. from Smith College, *summa cum laude*, J.D. from Harvard Law School, *cum laude*, and M.D. from New York University School of Medicine, where she was elected to Alpha Omega Alpha. She completed internship and residency in Internal Medicine and subspecialty training in Pulmonary Disease and Critical Care Medicine at Mount Sinai School of Medicine (MSSM), after which she joined the faculty of the Division of Pulmonary and Critical Care Medicine of MSSM's Department of Medicine and was appointed as Associate Director of the Medical Intensive Care Unit (MICU). She is also Associate Director of the Respiratory Care Unit (RCU), a model interdisciplinary program for research and clinical care of patients with chronic critical illness. Dr. Nelson advanced to the rank of Associate Professor in Medicine in 2002.

3.A.2. ***Clinical Research Career***. Although her early achievements as a molecular scientist and medical educator augured well for a future in basic research and/or teaching, Dr. Nelson's major investigative interests changed as a result of her clinical experience and in 1999 she decided to focus her career on palliative care for critically ill patients. This decision was motivated by her experiences working in the ICU setting, and particularly by her perception that symptom management, communication between patients/families and clinicians, and other aspects of palliative care for older adults requiring critical care, urgently needed improvement. Traditionally, intensive care and palliative care were viewed as sequential and mutually exclusive, with palliation deferred until attempts to prolong life were finally abandoned and death clearly seen as near. Dr. Nelson and others saw this model as fundamentally flawed, given limitations on our ability to predict outcomes of critically ill patients with certainty. In a series of papers in the *J Intensive Care Med*,[1,2] *Crit Care Med*,[3] and the *Ann Intern Med*,[4] she described a different paradigm, in which palliative care is an integral component of comprehensive care from the beginning of each patient's experience in the ICU. This was a

timely formulation, but Dr. Nelson recognized that more empirical study was required to support evidence-based practice under the new model. To meet this need, Dr. Nelson conceived a program of clinical research to improve palliative care for older adults with acute and chronic critical illness, in which she has been productively engaged for the past 4 years. The focus of Dr. Nelson's program on geriatric patients reflects their predominance in ICUs across the country and particularly in the chronically critically ill group. As a specialist in intensive care medicine and palliative medicine, Dr. Nelson brings an important perspective to this new area of inquiry and broadens the scope of aging research.

3.B. Career Goals and Objectives: Scientific Biography

This section describes the Candidate's overall career goal and her specific career objectives for the K02 period. Her development as an independent clinical investigator is traced, including her transition from a series of foundation awards for professional development and research to her first R01 grant this year. This section documents the Candidate's success in obtaining external funding for her research, describes the network of important collaborative relationships that she has developed, and demonstrates her strong potential with sufficient protected time for future contributions and research leadership in an area of increasing importance for our aging population. Finally, this section demonstrates the need for reduction through the K02 award of other, competing responsibilities, to allow the Candidate to achieve her research career objectives.

3.B.1. ***Career Objectives.*** Dr. Nelson's **overall career goal** is **to lead a strong, expansive, and sustainable research program that will continue to inform and improve palliative care for older adults with chronic critical illness**. She plans to use the K02 award to concentrate on the following **specific career objectives**: **1) Enhancement of her clinical research skills and knowledge**, with emphasis on sophisticated study design including interventional trials and large-scale projects, and on quantitative analytic methods; **2) Enhancement of her skills and knowledge in palliative medicine and geriatrics**, to improve her ability to design and conduct appropriate clinical studies at the intersections of palliative medicine, pulmonary/critical care medicine, and geriatrics; **3) Expansion of her research program beyond observational studies to trials of interventions** to improve palliative care during chronic critical illness; **4) utilization of advanced skills, knowledge and experience and of data emerging from her current R01 project to obtain additional R01 or comparable funding for interventional trials**. Dr. Nelson's career development plan, as described below, consists of advanced didactic training and intensive research activity on an increasing scale and level of complexity. Additional skills, knowledge, experience, and protected research time will enable her to obtain further independent funding for and to conduct interventional trials and other activities, which in turn will ensure the stability, sustainability, and ongoing success of Dr. Nelson's research program, and enhance her ability through research activity and leadership to promote improvement in the quality of palliative care for critically ill older adults.

3.B.2. ***Success as an Independent Investigator/Potential for Future Contributions***. Dr. Nelson successfully competed for the prestigious Faculty Scholar Award from the Soros Foundation Project on Death in America, which supported her professional development and research effort from 1999-2001. Specifically, the Soros Award funded the Candidate's study of the symptom experience of critically ill cancer patients receiving intensive care, which was published in 2001.[5] She then obtained funding from the Robert Wood Johnson Foundation (2000-2002) to lead a multicenter team in conducting a national survey of ICU directors about end-of-life care, which was recently presented at the American Thoracic Society International Symposium.[6] With additional support from the Geriatric Research and Education/Clinical Center based at Mount Sinai's affiliated Bronx VA Medical Center, Dr. Nelson conducted a pilot project studying the symptom burden of patients with chronic critical illness.[7] Data collected in this project formed the basis for the Candidate's R01 application to study symptom burden and associated outcomes of chronic critical illness, which was funded by NIA for 4 years beginning May 1, 2003 (R01 AG 21172-01 A2). Dr. Nelson is also the recent recipient of a Clinical Research Award from the American Lung Association (ALA), which supports a study of communication and decision-making about treatment for chronically critically ill patients. In addition, she has served as co-investigator and then consultant for an ongoing, two-phase, multicenter research project funded by the Robert Wood Johnson Foundation to develop, validate, and benchmark quality indicators for palliative care in the ICU.[8] **Table 1** summarizes externally-funded clinical research projects for which Dr. Nelson is Principal Investigator.

Table 1. Research Grants for which Dr. Nelson is Principal Investigator

Year	Title (Funding Source)	*Direct*
2003-2007	Symptoms/Associated Outcomes of Chronic Critical Illness (RO1 AG 21172-01 A2, NIA)	$800,000
2002-2004	When Critical Illness Becomes Chronic: Decision-Making in the Setting of Prolonged Mechanical Ventilation (American Lung Association)	$ 70,000
2000-2002	National Survey of ICU Directors About End-of-Life Care (Robert Wood Johnson Foundation)	$202,939
2002	Integration of Palliative Care/Intensive Care for Patients with Acute and Chronic Critical Illness- Roger C. Bone Advances in End-of-Life Care Award (CHEST Foundation – Amer. Coll. Chest Phys.)	$ 2,500
2000-2002	Pilot Project: Symptoms During Chronic Critical Illness (VA Geriatric Res./Edn./Clin. Center)	$100,000
1999-2001	Faculty Scholar Award, Project on Death in America (Soros Foundation, Open Society Institute)	$140,000

3.B.2.1. *Experience and Recognition*. Through this work, Dr. Nelson has gained experience in both quantitative and qualitative clinical research using several study designs (cohort study, survey, focus group/structured interview) and techniques for data collection and analysis. She has developed special expertise in assessment of comfort and communication needs of critically ill older adults and their families, which continues as the major focus of her research program. Dr. Nelson has played a pioneering role in the field of palliative care for patients with acute and chronic critical illness, contributing new empirical evidence as well as an influential theoretical framework to the scientific literature. National recognition of Dr. Nelson's contributions is reflected in her selection by the CHEST Foundation of the American College of Chest Physicians (ACCP) as the 2002 recipient of the Roger C. Bone Advances in End-of-Life Care Award, and a member of the Steering Committee of ACCP's End-of-Life Network; by the Society of Critical Care Medicine to receive the 2003 Grenvik Family Award for Ethics, and to lead the first national program on Chronic Critical Illness at the Society's annual International Symposium; as a member of the National Advisory Committee for Oregon Health & Science University's Palliative Care Program; by the Robert Wood Johnson Foundation as a Core Member of the Critical Care Peer Workgroup of Promoting Excellence in End-of-Life Care; and as a member of the National Consensus Project to Establish Palliative Care Standards.

3.B.2.2. *Collaborative Relationships*. Dr. Nelson has also been successful in establishing important collaborative relationships with research leaders in the fields of geriatrics, palliative care, and intensive care. At Mount Sinai, she continues to work closely with Drs. Sean Morrison and Diane Meier, who are renowned experts in geriatric palliative care research, and Dr. David Nierman, an acknowledged leader in the study of chronic critical illness and outcomes of critically ill older adults. She also collaborates with Dr. Sylvan Wallenstein, a senior biostatistician with experience on numerous projects in aging research. In addition, Dr. Nelson has ongoing collaborations with research colleagues across North America, including Drs. D. Cook (McMaster Univ.), D. Angus (Univ. of Pittsburgh), E. W. Ely (Vanderbilt Univ), J. R. Curtis (Univ. of Washington), M. Danis (NIH), R. Portenoy (Beth Israel Med. Ctr.), and M. Levy (Brown Univ.).

At Mount Sinai, Dr. Nelson has worked with colleagues in the Departments of Medicine and Nursing to develop the Respiratory Care Unit (RCU) for comprehensive, organized and standardized care of patients with chronic critical illness.[9-11] The multidisciplinary clinical/research program centered in the RCU is nationally recognized and serves as a strong foundation for the Candidate's research program, including the R01 project she commenced in May 2003. As described more fully in Section 5. below, the institution's research environment is highly stimulating and supportive, including the nation's leading Department of Geriatrics, a preeminent Palliative Care Institute, a K30 Clinical Research Training Program, a Master of Science in Public Health program, and abundant opportunities for productive collaborations in geriatric palliative care research.

3.B.3. ***Contribution of K02 Award***. Although Mount Sinai recognizes and values Dr. Nelson's research and other accomplishments and is committed to her professional development, this institution, like many academic institutions in the US, now requires faculty to support salary fully through externally-funded research, clinical, administrative, and/or teaching activities. The attached letters of Drs. Klotman (Department Chair) and Iannuzzi (Division Chief) reflect adherence to this policy by the Department of Medicine and the Division of Pulmonary and Critical Care Medicine, in which Dr. Nelson is appointed. At the present time, 40% of Dr. Nelson's effort is funded by research grants. Of that 40%, support for 25% effort in her current R01 will continue through April 2007, but support for the additional 10% (ALA Clinical Research Grant) and 5% effort (RWJ Foundation project) will terminate in July 2004 and June 2005 respectively. During this academic year (2003-04), Dr. Nelson will have approximately 6 months of clinical service, with additional time required for teaching and administration. This load will grow heavier over the next 2 years in the absence of additional

support for research professional development or effort. Without significantly more protected time, it will be impossible for Dr. Nelson to focus intensively on her academic growth and research program, as is required to achieve her career objectives and realize her full potential as an independent investigator and research leader. The years 1999-2001, when Dr. Nelson's effort was largely supported by a career development award from the Project on Death in America, saw rapid professional growth and productivity in all important areas, including successful applications for research funding, initiation of major research projects, and contributions to the scientific literature. It was during those years that Dr. Nelson conducted preliminary studies that served as the basis for her successful R01 application. A K02 award at this time would substantially reduce Dr. Nelson's non-research load, affording essential protected time for full utilization of the data and analyses from the R01 project recently funded by NIA and for further development of her research program and career. Drs. Davis (Dean and CEO), Klotman, and Iannuzzi have assured that Dr. Nelson will have 75% protected time for research and related activities throughout the K02 award. During this time, she will work actively to obtain additional federal and other extramural research funding (for example, two additional R01 grants as well as further foundation support), thereby ensuring the stability and sustainability of her program of aging research.

3.B.4. *Summary*. In summary, since embarking on her clinical research program in 1999, the Candidate has built a nationally recognized research program in a new field that she has helped to define. She has contributed new information and original conceptualization to the scientific literature. She has helped to broaden the field of geriatrics to include intensive care and palliative care, which are required primarily by older adults. She has also established a strong network of collaborative relationships with researchers at her own institution and others across North America. Building on a continuous track record of peer-reviewed research grants from foundations, Dr. Nelson has established herself as an independent investigator, now with R01 support from NIA. She has a clearly formulated plan for the future of her innovative research program, as described below. At this juncture, it is important for Dr. Nelson to focus intensively on enhancement of her program and career through acquisition of necessary additional knowledge and skills in clinical investigation, geriatrics and palliative medicine, practical experience in the design, conduct and leadership of more complex research, and additional R01 or comparable funding for projects testing interventions to improve palliative care for older adults. Whereas she currently carries substantial clinical, teaching, and administrative responsibilities, a K02 award would give the Candidate sufficient time protected from these responsibilities to solidify and expand her current research program and her role as a research leader.

3.C. Career Development Activities During Award Period

This section sets forth the Candidate's specific plan for research career development. The plan includes an intensive program of advanced training and research focus that will enhance her role as Principal Investigator of the recently funded R01 project, enable the Candidate to use her current observational research as a platform for successful applications for federal funding of interventional research, and establish her as a research leader of international stature. The guiding role of senior colleagues renowned for their geriatric palliative care research and program leadership is discussed. Milestones for the Candidate's career development over the K02 period are specified.

3.C.1. *Overview*. As recommended for optimal adult learning,[12] the Candidate's career development plan has been shaped by her own experiences as an investigator and clinician, and by her career objectives, in a process of formative appraisal and rigorous assessment of her individual learning needs. This plan is shown in **Appendix A**, which indicates the time to be devoted to each component. To date, Dr. Nelson has had limited formal training in clinical research and experience only in observational studies. In addition, although she has acquired considerable experience in clinical care of older adults with acute and chronic critical illness and other geriatric patients with palliative needs, Dr. Nelson has not been formally trained in geriatrics or palliative medicine. With protected time provided by this award, she will devote herself intensively to a program of didactic research training, enhancement of skills and knowledge in geriatrics and palliative medicine, guided experience in project management and research leadership, and direct, practical application of new expertise in research of increasing complexity, sophistication and scope. Skills and knowledge in these complementary areas will be incorporated in Dr. Nelson's ongoing and future research. Over the period of the award, Dr. Nelson will use this training and experience to enhance her current R01 and enable her to obtain additional R01 or comparable funding for projects building on the present research. The K02 award will permit Dr. Nelson to strengthen and diversify her clinical research program, facilitating her transition from a newly independent

investigator with a single R01 to a leader of multiple, federally-funded interventional trials to improve palliative care of older adults with acute and chronic critical illness.

3.C.2. *Training and Incorporation of New Expertise in Ongoing and Future Research*.

3.C.2.1. *Training in Clinical Research*. As outlined in **Table 2**, clinical research coursework will focus on biostatistical methods, interventional trial design, and data management, and will be concentrated in the first three years of the K02 so that Dr. Nelson can incorporate this learning as Principal Investigator of the present R01 project.

Table 2: Proposed Further Coursework Serving Candidate's Career Objectives and Research Aims*

COURSE	TOPICS/DESCRIPTION (RELEVANCE)
Year 1: (2004-5)	
Introduction to Data Management (MSSM-MPH, EPB400: 1 credit, Fall)	Data entry and storage; statistical functions for data cleaning and exploration; importation of data into statistical analysis software programs. **(Career Obj. 1, R01 Research Aims 1-2**)
Core Topics in Geriatric Medicine (MSSM, Department of Geriatrics and Adult Development, Fall)	Four-month weekly series of seminars covering core clinical topics in geriatric medicine. **(Career Obj. 2, Interventional Research)**
Multivariable Methods (MSSM-MPH, EPB600: 2.5 credits, Winter)	Multivariable linear regression, including tests of model fit, regression diagnostics, representation of categorical independent variables and transformations of dependent variables; logistic regression; Cox proportional hazards models. **(Career Obj. 1, R01 Research Aim 2)**
Topics in Biometry (Columbia Univ., P8110: 3 credits, Spring)	Estimation and comparison of survival curves, regression models for survival data, log-linear models, logit models, analysis of repeated measurements, and analysis of data from blocked and split-plot experiments. **(Career Obj. 1, R01 Research Aim 2)**
Year 2: (2005-6)	
Professionalism and Ethical Issues in Clinical Research (MSSM-K30/MPH, CLR510: 1.5 credits, Fall)	Justification of human research and reasonable risk, validity of clinical trials, conflict of interest and funding of research, scientific fraud, scientific community and mentoring, authorship and attribution. **(Career Obj. 1, R01 Research Aims 1-2)**
The Randomized Clinical Trial (Columbia Univ., P8140: 2 credits, Spring)	Protocol development, randomization, blindedness, recruitment, informed consent, sample size determination, crossover and collaborative trials. **(Career Obj. 1, Interventional Research**)
Harvard Medical School Program in Palliative Care Education and Practice (1 week, Spring)	Intensive course, first of 2 one-week blocks. Assessment/management of distressing symptoms and delirium, range of other important topics in palliative medicine. **(Career Obj. 2, R01 Research Aims 1-2, Interventional Research)**
Palliative Care Rotation (Memorial Sloan-Kettering Cancer Center: 1 week, Spring)	Academic clinical training in palliative medicine, under supervision of world-renowned experts in symptom management, including K. Foley, MD. **(Career Obj. 2, R01 Research Aims 1-2, Interventional Research)**
Year 3: (2006-7)	
Advanced Multivariate Techniques and Applications (Columbia Univ., P9104: 4 credits, Fall)	Multivariate analysis of variance, discriminant function analysis, canonical correlation analysis, principal components and factor analysis, analysis of covariance structures. **(Career Obj. 1, R01 Research Aim 2)**
Harvard Medical School Program in Palliative Care Education and Practice (1 week, Fall)	Second of 2 one-week blocks, described in Year 2 above. **(Career Obj. 2, R01 Research Aims 1-2, Interventional Research)**
Introduction to Informatics (MSSM-MPH, CLR540: 2 credits, Winter)	Clinical research applications of informatics, including methods for capture, storage, and retrieval of clinical data and information system support for research interventions. **(Career Obj. 1, Interventional Research)**
Palliative Care Rotation (Beth Israel Medical Center: 1 week, Spring)	Further academic clinical training in palliative medicine, under supervision of R. Portenoy, MD **(Career Obj. 2, R01 Research Aims 1-2, Interventional Research)**

*****MSSM = Mount Sinai School of Medicine; MPH = Master of Public Health in Community Medicine Program, MSSM; K30 = K30 Clinical Research Training Program, MSSM; Career Obj. = Career Objective as set forth in Section 3.B.1. of text; R01 Research Aims = Specific aims of R01 project (AG 21172-01 A2) recently funded by NIA, as described in Section 6.A.3. of text.

She will take full advantage of resources locally available through Mount Sinai's K30 Clinical Research Training Program and Master of Public Health in Community Medicine Program, as well as additional offerings

at the School of Public Health of nearby Columbia University. Courses for which credit is available will be taken for credit. Completion of coursework in complex data management and multivariable analysis will coincide with the conduct of the main analyses of data collected in Dr. Nelson's ongoing R01 project, and will permit her to play a more active and effective role in collaboration with the biostatistician and senior co-investigators, particularly for the statistical modeling planned under Aim 2 of that project. This training and experience, together with planned study of interventional research methods, and of geriatrics and palliative medicine as described below, will also enable Dr. Nelson to use the results of her ongoing observational research as a basis for development and rigorous evaluation of interventions to improve the quality of palliative care for older adults. By the end of the K02 period, Dr. Nelson will be substantially better qualified to conduct interventional trials for which R01 funding will be sought during the award period.

3.C.2.2. *Training in Geriatrics and Palliative Medicine*. The Department of Geriatrics at Mount Sinai and its Hertzberg Palliative Care Institute are renowned centers for research, education, and clinical care, and will provide Dr. Nelson with an ideal environment for career development during the K02 award. At present, the Candidate's clinical, teaching, and administrative responsibilities in the Department of Medicine preclude significant participation in the many offerings and activities of the Geriatrics Department and Palliative Care Institute. With reduction of these responsibilities, Dr. Nelson will have time she needs to participate regularly in diverse activities that are relevant for her research and career development, including attendance at grand rounds, research seminars, clinical conferences, educational sessions, and journal clubs in geriatrics and in palliative care. In Year 1 of the award, for example, she will attend a 4-month series of weekly seminars covering core topics in geriatric medicine. Dr. Nelson will also spend an additional two weeks during the first two years of the award attending on Mount Sinai's Palliative Care Consultation Service. In addition, she will obtain advanced training in palliative medicine in an intensive program at Harvard Medical School and in rotations at two other preeminent palliative care programs in New York City, Memorial Sloan-Kettering Cancer Center (Candidate will work with Dr. Kathleen Foley) and Beth Israel Medical Center (work with Dr. Russell Portenoy). The Candidate has already been accepted to these programs, which are recognized for rigorous education by acknowledged experts. These activities will help to prepare her for the certification examination in Palliative Medicine, which she plans to take in Year 3 of the K02 award, as well as for the development of further research projects at the intersections of palliative medicine, geriatrics, and intensive care.

3.C.2.3. *Project Management and Research Leadership*. Throughout the K02 period, Dr. Nelson will have expert guidance from two senior faculty in Mount Sinai's Department of Geriatrics, Drs. Sean Morrison and Diane Meier. Both Dr. Morrison and Dr. Meier are international leaders in geriatric palliative care, both have demonstrated a strong and sustained commitment to the development of Dr. Nelson's research career, and both are active collaborators in her ongoing research including her current R01 project. With Dr. Morrison, who will meet at least twice each month with Dr. Nelson during the K02 period, she will focus on project management skills and on the expansion of her research program to include interventional and larger-scale studies. He is a recognized expert in these areas and specifically in symptom intervention research, with a solid record of R01 awards from the Agency for Healthcare Research and Quality and NIA, as well as numerous foundation grants. In addition, Dr. Morrison is Director of Research for the Hertzberg Palliative Care Institute. He recently received from NIA a 5-year K24 Mid-Career Investigator Award in Patient-Oriented Research specifically to mentor investigators including Dr. Nelson in the continuing development of research careers in geriatric palliative care. As a senior collaborator on the present R01 project and others, Dr. Morrison will assist in application of Dr. Nelson's expanding knowledge of biostatistical and psychometric methods during the analytic phase of the R01 project and future projects testing symptom interventions during the K02 period.

Together with Dr. Morrison, Dr. Meier will counsel as well as collaborate with Dr. Nelson in her further development as a research leader. Dr. Meier is Director of the Hertzberg Palliative Care Institute and of the Center to Advance Palliative Care, a national initiative of the Robert Wood Johnson Foundation. She has world recognition for both research and program development in palliative care and aging, and is the recipient of an Academic Career Leadership Award (K07) from NIA to promote training and career development of faculty including Dr. Nelson. During the K02, Dr. Meier will meet with Dr. Nelson at least monthly, providing critical feedback and role-modeling of leadership skills, and senior guidance in areas including organization of a research program encompassing geriatrics and palliative care as well as critical care, participation in a worldwide network of research colleagues in these fields, and management of other institutional commitments in a way that maximizes research productivity. Like Dr. Morrison, Dr. Meier is a senior collaborator on the

Candidate's current R01 project and looks forward to continued collaboration with her on future projects as Dr. Nelson's research program expands.

3.C.3. ***Milestones for Career Development Progress of Dr. Nelson*****.** **Table 3** sets forth milestones that Dr. Nelson plans to achieve in the development of her research career during the K02 period.

Table 3. Milestones for Candidate's Further Research Career Development During K02 Period

By end of Year 1 (2004-5):

- Have new skills/knowledge/experience in project and data management, multivariable regression, other biostatistical methods and aspects of aging that are relevant to the present R01 and future research in development;
- Apply new learning to present R01 (and other ongoing research): direct data cleaning, explore emerging data in project databases, refine and adjust analytic methods, collaborate more effectively with biostatistician and other co-investigators;
- Use emerging R01 findings to inform further development of protocols for pilot interventional trials, and complete 1 pilot study;
- Complete 3 to 4 first-authored manuscripts for peer-reviewed publications (to include reports of preliminary findings from the first 2 years of the present R01 and from other research by the Candidate).

By end of Year 2 (2005-6):

- Have new skills/knowledge/experience in clinical research methods (including randomized trials and responsible conduct of research), palliative medicine, and geriatrics;
- Apply new learning in preliminary analyses of findings of present R01 and first pilot study, and conceptualization of new interventional trial based on current R01 and first pilot for which R01 funding will be sought;
- Prepare application for R01 or comparable funding for interventional trial (based on pilot #1);
- Complete second pilot interventional study;
- Complete 3 to 5 additional manuscripts for peer-reviewed publications (to include reports relating to present R01 and other research).

By end of Year 3 (2006-7):

- Have further skills/knowledge/experience in clinical research methods (including principal components and factor analysis, and informatics applications) and in palliative medicine and geriatrics;
- Obtain certification in Palliative Medicine from American Board of Hospice and Palliative Medicine;
- Complete original R01 project (4/07);
- Have new R01 or comparable funding for first interventional research project;
- Apply new learning to final analysis of findings of original R01 and pilot #2, initiation of first full-scale interventional project, and conceptualization of second interventional project;
- Prepare additional application for R01 or comparable funding for second interventional trial (based on pilot #2)
- Complete 3 to 5 additional manuscripts for peer-reviewed publications, including reports relating to original R01 project and interventional studies.

By end of Year 4 (2007-8):

- Have substantially more experience and expertise in planning, conducting, managing, and analyzing rigorous and ethically-appropriate clinical research, including interventional trials and sophisticated studies on a large scale;
- Have new R01 or comparable funding for second interventional research project;
- Apply new expertise and experience to ongoing interventional projects and conceptualization of further development of research program;
- Complete 3 to 5 additional manuscripts, including reports relating to interventional studies and other research.

By end of Year 5 (2008-9):

- Have a strong, expansive, and sustainable research program to improve palliative care for older adults with chronic critical illness, including multiple R01 or comparable grants for interventional studies;
- Have well-developed skills in clinical research methods, palliative medicine, and aspects of aging relevant to this program;
- Have an expanded network of strong and effective relationships with research collaborators;
- Complete additional manuscripts;
- Achieve international stature as a research leader.

5. ENVIRONMENTAL AND INSTITUTIONAL COMMITMENT TO THE CANDIDATE

5.A. Description of Institutional Environment

As reflected in the Resources description (pp. 9-11 above) and the attached letters of Drs. Davis, Klotman, Siu, Iannuzzi, Meier and Morrison (Appendix B), Mount Sinai School of Medicine and Mount Sinai Hospital provide a stimulating and supportive environment for further development of Dr. Nelson's career as an independent investigator. This environment encompasses the following:

- An internationally recognized program for research, education, and clinical initiatives in geriatric palliative care. Led by Drs. Sean Morrison and Diane Meier (Dr. Nelson's research collaborators and senior mentors), this program involves 14 faculty and is supported by the Hertzberg Palliative Care Institute in the Department of Geriatrics and by the Center to Advance Palliative Care in Hospitals and Health Systems, a national initiative of the Robert Wood Johnson Foundation;

- A renowned research and clinical program focused specifically on patients with chronic critical illness. Key faculty in this program include Dr. David Nierman, an acknowledged expert in chronic critical illness and a close collaborator of Dr. Nelson. The program is based in the Respiratory Care Unit of Mount Sinai Hospital, which admits approximately 175 patients each year and is considered a center of excellence for care of the chronically critically ill.

- Active and highly successful programs of clinical (and basic science) research in a number of departments, including Medicine and Geriatrics. Faculty in these departments are conducting research with support from many R01, K24, K23, and other NIH grants; total research funding for Medicine and Geriatrics exceeds $37.5 million and $24 million respectively. An array of research conferences, seminars, and journal clubs is regularly available across the institution including in the Department of Geriatrics (and Hertzberg Palliative Care Institute) and the Division of Pulmonary and Critical Care Medicine of the Department of Medicine. Inter- and intra-departmental collaborations abound and the School of Medicine commands a strong clinical research infrastructure. Career development of clinical researchers through training, mentoring, access to infrastructure and other support is a high priority of the institution and specifically of the Department of Medicine, in which the Candidate holds her faculty appointment.

- A Geriatric Research and Education/Clinical Center (GRECC) based at Mount Sinai's affiliated Bronx Veterans' Administration Medical Center. This Center has supported a wide range of geriatric research including Dr. Nelson's pilot investigation of symptom burden in chronic critical illness. A major focus of the GRECC is geriatric palliative care research. The GRECC is closely tied to the Department of Geriatrics at Mount Sinai through multiple connections including leadership of both the Department and the GRECC by Drs. Albert Siu and Sean Morrison, who are strongly committed to the success of Dr. Nelson's research and career development.

- A K30-funded program for training of clinical investigators, including a comprehensive curriculum in clinical research methods, epidemiology and biostatistics, data management, and research ethics. The Program Director is Dr. Janice Gabrilove, who is also Vice Chair for Clinical Research in the Department of Medicine; Dr. Siu is Co-Director of the K30 Program.

- A Master of Public Health Program in the Department of Community Medicine, which is a national leader, chaired by Dr. Philip Landrigan. Courses in this program, which offers didactic training in more advanced biostatistical methods, are available for credit without matriculation for the masters degree.

- A large, university-affiliated teaching hospital that cares for a diverse population of more than 40,000 inpatients each year, including approximately 8,000 critically ill patients (the majority of whom are older adults) admitted to five adult intensive care units. Patients with chronic critical illness are transferred from these ICUs to the Respiratory Care Unit described above. The hospital is part of a large health system encompassing an extensive regional network of affiliates.

5.B. Institutional Commitment to the Candidate's Research Career Development

The institution's strong commitment to and enthusiastic support for Dr. Nelson's career development and research program are reflected in the attached letters (**Appendix B**) of Drs. Davis (Dean, President and CEO), Klotman (Department of Medicine Chair), Iannuzzi (Division Chief), Siu (Department of Geriatrics Chair), Morrison (Vice Chair for Research, Department of Geriatrics; Research Director, Hertzberg Palliative Care Institute), and Meier (Division Chief for Geriatrics, Department of Medicine; Director, Hertzberg Palliative Care Institute). The responsible institutional leaders provide assurance that with the K02 award, Dr. Nelson will have adequate time to pursue her career development and research plans, and access to all facilities and resources that will promote the further development of her research program. At least 75% of Dr. Nelson's effort will be protected by the K02 award for research and research career development. This will continue

throughout the award period, with corresponding limitation of her clinical, teaching, and administrative responsibilities. Dr. Nelson is assured of a full-time academic appointment and all associated rights and privileges for the duration of the K02, and will continue to receive a commensurate salary that is not contingent upon receipt of this award.

6. RESEARCH PLAN

6.A. Statement of Hypotheses and Specific Career and Research Aims

A large and growing population of patients survives acute critical illness only to become "chronically critically ill," with profound debilitation and prolonged dependence on mechanical ventilation and other specialized care. In the US, this group already exceeds 100,000 patients annually, the majority of whom are over age 65. Costs of care for patients with chronic critical illness are estimated at $15 billion, attributable mainly to older adults. Despite aggressive and resource-intensive medical treatment, outcomes for these patients remain poor, with high rates of in-patient and early post-discharge mortality or extreme functional dependence among survivors. The Candidate for this K02 award has recently received R01 funding (AG 21172-01 A2) from NIA to study the symptom burden of older adults with chronic critical illness and investigate associations between symptom experience and other outcomes of chronic critical illness and prolonged mechanical ventilation. She has been a pioneer in this field of inquiry and now proposes to use time protected by the K02 award to solidify and expand her program of research and her role as a research leader.

6.A.1. ***Hypotheses*****:** The Candidate's research program and this proposal address the following **hypotheses**: **(A) Distressing physical and psychological symptoms are common among patients with chronic critical illness and are associated with an increased risk of adverse clinical and utilization outcomes** including higher mortality, a lower rate of liberation from mechanical ventilation, and poorer functional status (hypothesis tested in Dr. Nelson's newly funded R01 project); **(B) Improved palliative care including successful treatment of symptom distress will improve important outcomes of chronic critical illness** (hypothesis driving further development of Candidate's program to include interventional research).

6.A.2. ***Specific Career Aims***: The Candidate's ***overall career objective*** is **to lead a strong, expansive, and sustainable research program that will continue to inform and improve palliative care for older adults with chronic critical illness**. Building on a track record of foundation funding over a several year period, she obtained her first R01 grant this year. This newly-funded R01 project will serve as a springboard for achievement of Dr. Nelson's ***main career goals for the period of the K02 award*** she now seeks, which are: ***i*. to expand and diversify her research program to encompass multiple, federally-funded projects on a similar or larger scale; *ii*. to move beyond observational to interventional research including major randomized, controlled trials; *iii*. to secure additional and continuous federal funding for this program of clinical investigation**; and ***iv***. **to make a successful transition from newly-independent scientist to research leader.** For Dr. Nelson, who would otherwise carry significant clinical, teaching, and administrative responsibilities, the K02 award will provide essential protected time to focus on these goals and her ongoing research.

As reflected in the discussion of Career Objectives (Section 3.B.1.) and the Career Development Plan (Section 3.C.), Dr. Nelson plans to pursue her career goals during the K02 period through the following ***specific career aims***:

1) ***To obtain advanced skills and knowledge in clinical research, palliative medicine and geriatrics***. The Candidate's program of training will emphasize sophisticated study design including randomized, controlled trials, quantitative analytic methods, project management, and topics of particular relevance to aging research. This training will be obtained in a curriculum tailored to meet her individual needs, including didactic coursework at a masters level and involvement in a diverse range of activities sponsored by Mount Sinai's Department of Geriatrics. In addition, the Candidate will enhance her knowledge of palliative medicine. The funded R01 project will provide a context for acquisition and application of new knowledge and skills. In her further development as a research leader, the Candidate will be guided by two internationally-recognized leaders in aging research and palliative care, who are senior co-investigators on this project and will continue to collaborate with Dr. Nelson in future research.

2) ***To obtain R01 or comparable funding for research projects testing interventions to improve palliative care for older adults with chronic critical illness***. The present R01 project will provide robust new data about the symptom experience of chronically critically ill patients and analyses of associations between symptom burden and other important outcomes of chronic critical illness and prolonged mechanical ventilation. During the K02 period, emerging results from the R01 project and from pilot interventional studies building on those results will provide the basis for applications for federal funding to conduct randomized, controlled trials of interventions to improve palliative care for older adults with chronic critical illness.

6.A.3. *Specific Research Aims of the Newly Funded RO1 Project*:

The Candidate's newly funded R01 project will advance the development of her research career by providing both practical experience and empirical evidence to be used in the expansion and diversification of her program of clinical investigation. Conversely, achievement of the Candidate's career aims for the K02 award will maximize her effectiveness and productivity as Principal Investigator of this R01 project, by providing relevant skills and knowledge as well as sufficient protected time to concentrate on this research and its implications for further studies. ***Specific Aims*** of the ongoing R01 project are the following:

1) ***To determine the prevalence and characteristics of distressing symptoms during chronic critical illness.*** Research under this specific aim investigates the hypothesis that multiple distressing symptoms are common during chronic critical illness. This research will identify through direct, real-time, patient self-reports, symptoms that are prevalent and distressing for chronically critically ill patients, so that these symptoms can be specifically targeted for interventions to improve symptom experience and other outcomes associated with symptom burden.

2) ***To evaluate the influence of symptom distress on important outcomes of chronic critical illness.*** Research under this aim tests the hypothesis that symptom burden adversely influences clinical and utilization outcomes including success in liberation from the ventilator, time to ventilator independence, and vital and functional status. This research evaluates the association of symptom distress with important outcomes of chronic critical illness, in order ultimately to improve those outcomes as well as patient comfort through targeted interventions to reduce symptom distress.

The Candidate is conducting this research as a prospective cohort study of chronically critically ill patients in the Mount Sinai Hospital Respiratory Care Unit. Using a validated and practical symptom assessment instrument, we assess physical and psychological symptoms bi-weekly through patient self-reports. We also collect data with respect to selected patient attributes and care processes that may influence outcomes of interest. Prevalence and characteristics of symptoms will be analyzed. Statistical modeling will be used to evaluate associations between symptom burden and selected other clinical and utilization outcomes. As has recently been demonstrated for cancer pain, rigorous studies of prevalence and intensity of symptom distress are a necessary precondition and strong impetus for quality improvement interventions. The Candidate will use data and analyses from this observational research, together with advanced research skills, knowledge, experience and protected time provided by the K02 award, to develop targeted interventions to improve symptom experience and associated outcomes of older adults with chronic critical illness. During the K02 period, Dr. Nelson will seek R01 or comparable funding for randomized, controlled interventional trials. After description of the present R01 project in Section 6.D. below, Section 6.D.8.1. describes a proposed pilot interventional study that would build on the ongoing symptom research and support an application for federal funding for a full-scale interventional trial.

6.B. Background, Significance, and Rationale

6.B.1. *Chronic Critical Illness Among Older Adults: A Serious and Growing National Health Problem*.

Among 5 million patients admitted to ICUs in the United States each year, the majority are older than 65 years.[13] This proportion is expected to increase in coming decades with the aging of the population and expanding application of critical care treatments to older adults.[13] Although ICU treatment is effective for many of these patients, others survive acute critical illness only to become "chronically critically ill,"[9,14-18] with profound debilitation and continuing dependence on life-sustaining technology. Chronic critical illness is now recognized as a discrete syndrome rather than a simple prolongation of acute critical illness.[9] Weaning of chronically critically ill patients from mechanical ventilation is typically difficult and protracted, requiring

multidisciplinary expertise, extraordinary commitment on the part of caregivers, and many weeks to months of resource-intensive treatment.[19] These patients are increasingly treated in specialized units in acute care hospitals, such as the Respiratory Care Unit at this institution,[10,11] and similar units in other hospitals, long-term acute care facilities or weaning centers.[17,18,20-22] Unfortunately, even the most dedicated, organized and technologically advanced treatment often fails to avoid long-term ventilator dependence and/or poor survival.

The chronically critically ill patient group consists mainly of older adults and is rapidly growing. Data are available with respect to Diagnosis Related Group (DRG) 483,[23] which applies to hospitalized patients who have undergone tracheostomy for any indication other than disease involving the head or neck and was created by the Health Care Financing Administration to permit appropriate reimbursement for patients receiving prolonged mechanical ventilation.[24] Tracheostomy for failure to be liberated from mechanical ventilation after acute critical illness is increasingly accepted as a defining characteristic of chronic critical illness.[9,25] Median age for DRG 483 is 66 years, and the median age of those 65 years or older is 75.[26] Between 1993 and 1997, the number of Medicare discharges in DRG 483 rose from 69,773 to 86,293 nationally, an overall increase of nearly 25%.[27] The rate of increase has continued to rise, suggesting that the population of chronically critically ill patients already exceeds 100,000 annually.[25]

6.B.2. ***High costs and poor outcomes***. The intense level of health care required by chronically critically ill patients has an enormous impact on resource utilization and costs, but disappointing results in terms of patient outcomes. Mean length of stay for patients in DRG 483 is approximately 40 days.[26] Nationally, charges for these patients approach $15 billion, more than half of which is attributable to patients aged 65 and older.[26] Rates of hospital and early post-discharge mortality remain high, and extreme functional dependence is common among survivors. In New York State, hospital death rates are almost 50% for patients in DRG 483, with significantly higher mortality rates among patients $\geq$ 70 years.[24,27,28] Among critically ill patients in the APACHE database, 50% who were mechanically ventilated for $\geq$ 7 days died before hospital discharge.[29] Swinburne et al.[30] found that hospital mortality among older adults requiring more than 15 days of mechanical ventilation exceeded 90%. One-year mortality of Medicare patients surviving prolonged mechanical ventilation has been found to exceed 85%.[16,31,32] Recent research[33] documents poor outcomes at early post-discharge time points among patients ventilated in ICUs for a median of 8.6 days, a much shorter period than the typical duration of ventilator dependence for the chronically critically ill. Spicher and White[32] studied hospitalized patients requiring mechanical ventilation for $\geq$ 10 days, among whom over 70% were dead at 1 year after hospital discharge; only 3% of hospital survivors had no functional deficit at 1 year, 40% were institutionalized and an additional 30% were homebound requiring significant assistance. Studies focusing specifically on patients with chronic critical illness show that prospects for functional survival are dismal: only 11% of patients (mean age 66 years) who survived treatment for chronic critical illness in an extended care facility were at home with "good physical functionality" at 1 year after discharge.[21] Less than 10% of another elderly group of chronically critically ill patients were fully functional at 1 year after admission to a long-term acute care facility, while the remainder had significant functional impairments and dependence.[17]

6.B.3. ***Patient Suffering***. Chronic critical illness is a new field,[9] in which research to date has focused mainly on cost and resource efficiencies, success in liberation from mechanical ventilation, and survival. Apart from the Candidate's work, palliative care needs of chronically critically ill patients have received little research attention. However, existing evidence including Dr. Nelson's preliminary data suggests that chronic critical illness is typically accompanied by substantial patient suffering.[7]

Potential sources of suffering for chronically critically ill patients are many and varied. Symptom burden may be worsened by factors relating to the underlying critical illness and co-morbidities, to diagnostic and therapeutic interventions, to the physical environment of the care setting, and to unique psychological stressors including impaired communication due to endotracheal intubation, limited visitation, sleep deprivation, and protracted hospitalization.[1] Routine respiratory care and simply turning in bed can be extremely painful.[34-36] Small, exploratory, and retrospective studies of patients with acute critical illness have described a variety of symptoms, including pain, discomfort, dyspnea, anxiety, fear, sleep disturbance, depression, and distress due to difficulty in communicating.[37] Patients ventilated for short periods described dyspnea even during full ventilator support.[38,39] In the Candidate's study of cancer patients receiving ICU treatment for acute critical illness, many patients self-reported multiple, distressing physical and psychological symptoms at significant levels of severity.[5] These studies have served as a foundation for the R01 project that she is currently conducting, which for the first time assesses systematically and prospectively through direct, "real time" self-reports the symptom

burden for a large cohort of patients with chronic critical illness. Preliminary data we have gathered from chronically critically ill patients[7] (Section 6.C.) suggest that unrelieved symptoms are common and distressing in this clinical setting.

6.B.4. ***Association of Symptom Distress With Adverse Clinical and Utilization Outcomes of Chronic Critical Illness***. Symptom distress has been associated with adverse outcomes for patients and for health care systems. In various groups including patients with cardiovascular disease, cancer, or acute critical illness, associations between symptom burden and outcomes including survival, functional status, and quality of life have been documented.[40-49] Symptom assessment, particularly through patient-self-reports, has been shown to contribute significant prognostic information that is independent of other clinical predictors.[43,46,47,50,51] Previous research focusing specifically on outcomes of the chronically critically ill has identified factors including age, baseline functional status, and co-morbid illnesses as predictive variables,[17,18] but symptom burden has not been included in these analyses. A major objective of the Candidate's current R01 project is to explore the relationships between symptom experience and other outcomes of older adults with chronic critical illness, including the association of various symptom parameters with success in liberation from mechanical ventilation, time to ventilator independence, complications during treatment, functional status, and mortality.

Several possible mechanisms might underlie such associations in the setting of chronic critical illness. First, unrelieved symptoms elicit physiologic responses that are predominantly maladaptive, increasing myocardial oxygen consumption and deranging coagulation, immunity, and electrolyte balance.[39,52-57] Physiologic stress may also promote protein catabolism and proinflammatory cytokine expression, causing nitrogen wasting, muscle weakness and an ongoing systemic inflammatory response;[55] cachexia and severe protein malnutrition are among the most morbid conditions in chronic critical illness, predisposing the patients to numerous other complications including poor wound healing, sepsis, and persistent respiratory failure. Inanition from depression, nausea and other symptoms may worsen nutritional status and compound its adverse effects, particularly for older adults.[58] In addition, symptom distress may limit the ability of patients to cooperate in pulmonary hygiene, weaning, physical therapy, and other rehabilitative methods.[39,59]

Conversely, evidence exists that, besides providing comfort, treatment to control symptoms may reduce energy expenditure and improve hemodynamic status, pulmonary and other organ function, weaning success, and efficient resource use.[49,54,56,60-62] Administration of opioids decreases both oxygen consumption and carbon dioxide production in mechanically ventilated patients, with overall decreases in energy expenditure.[63] This may be advantageous in chronically critically ill patients with diminished cardiovascular and pulmonary reserve, who have hypermetabolism and hypercatabolism that is driven by persistent systemic inflammation and that is often refractory even to aggressive nutritional support. Treatment of anxiety and depression may shorten the time to liberation from mechanical ventilation.[61,62,64] At the same time, potential adverse effects of symptom treatment, such as excessive sedation or respiratory depression, with consequent prolongation of ventilator dependence or other complications, must also be carefully considered. Analyses planned in the Candidate's current R01 project will provide new information about these important interactions and relationships, allowing evidence-based development of interventions that target prevalent symptoms associated with both substantial distress and other clinically important outcomes.

6.C. Preliminary Studies and Results

6.C.1. ***The Mount Sinai Respiratory Care Unit***. We have collected preliminary data about symptom burden and other outcomes of chronic critical illness among patients in our Respiratory Care Unit (RCU), which accepts hemodynamically stable, mechanically-ventilated patients with chronic critical illness from all adult ICUs (Medical ICU, Surgical ICU, Cardiothoracic Surgical ICU, Cardiac Care Unit, Neurosurgical ICU) in this hospital. Approximately 175 patients are admitted annually to the RCU's 14 beds. Staffing is by nurses in a 3 to 1 patient to nurse ratio, under the supervision of primary attending physicians in collaboration with nurse practitioners on the RCU day and night; specific physicians with expertise in pulmonary/critical care medicine, nutrition/metabolic support, psychiatry, rehabilitation, neurology, or wound healing serve as consultants. Patients admitted to the RCU remain there until a final ventilator disposition is made, that is, until successful liberation from the ventilator or a clinical determination that further efforts to achieve ventilator independence will not succeed, or until death; generally, a one-month therapeutic trial is deemed to be adequate and average length of RCU stay is approximately 4 weeks. Patients who fail to be liberated from the ventilator are not transferred from the RCU to other facilities for additional attempts to wean them from mechanical ventilation,

but, rather, are discharged to skilled nursing facilities, to a regular hospital bed, or (rarely) to home. Our RCU is a model clinical and research program, which is nationally recognized.[9-11]

6.C.2. ***Preliminary Study Patient Group***. Eligibility for this preliminary study was established by the placement of a tracheotomy and transfer to the RCU for failure to wean from mechanical ventilation in an adult ICU at Mount Sinai; we excluded patients with a prior history of RCU treatment or ventilator dependence, and those with insufficient proficiency in English. Among 61 eligible patients who were consecutively admitted to the RCU, 50 patients were enrolled; consent was refused for 7 patients, no surrogate could be identified for 3 patients lacking decisional capacity, and 1 patient expired before consent could be obtained. Characteristics of the preliminary study patients are contained in **Table 4**. Like the national population of chronically critically ill patients, our preliminary study group consisted mainly of older adults, with a median age of 73. Most patients (86%) were living at home before the hospitalization, but many had chronic, co-morbid medical conditions upon which acute co-morbidities were superimposed. Most already had long stays in the hospital prior to RCU admission (median length of ICU stay was 15 days, median overall hospital stay including the period of RCU treatment exceeded 50 days).

Table 4. Characteristics of Chronically Critically Ill Patients: Preliminary Study Group (N=50)

Median age, yrs (range)	73 (21-97)
Male, no. (%)	26 (52)
Race/Ethnicity, no. (%)	
White, non-Hispanic	32 (64)
Black, non-Hispanic	13 (26)
Hispanic	4 (8)
Other	1 (2)
Residence Before Hospital Admission, no. (%)	
Home	43 (86)
Skilled Nursing Facility	7 (14)
Functional Independence Measure[68] (Motor Domain) Score at Hospital Admission, mean ± S.D.	75.2 ± 24.5[a]
Cognitive Status	
History of Dementia, no. (%)	6 (12)
Cognitively impaired (at study entry), no. (%)	39 (82)[b]
Delirious by Confusion Assessment Method for the ICU[75-76] (at study entry), no. (%)	13 (46)[c]
Primary ICU Admitting Diagnosis, no. (%)	
Cardiovascular	7 (14)
Pulmonary	14 (28)
Neurologic	7 (14)
Surgical	17 (34)
Other	5 (10)
ICU Transferring to RCU, no. (%)	
Medical ICU	24
Surgical ICU	14
Cardiothoracic ICU	1
Neurosurgical ICU	9
Cardiac Care Unit	2
Charlson Co-Morbidity Index Score,[67] mean ± S.D.	2.2 ± 1.9
APACHE II Score[d] (at study entry), mean ± S.D.	20.2 ± 4.9
ICU Length of Stay, median (range) no. days	15.0 (1-77)

[a]N = 46 (4 patients were unable to provide information and lacked surrogates). Score is given for the motor domain of the Functional Independence Measure.[68] [b]Defined as score > 10 on Six-Item Orientation-Memory-Concentration Test[69] (n = 10) or lacking sufficient cognitive capacity to respond to cognitive screen (n = 29); 3 others refused. [c]N = 28. 20 patients had stupor or coma preventing administration of the Confusion Assessment Method for the ICU,[75,76] 2 others refused. [d]APACHE II[70] score calculated at study entry using physiologic data from the previous 24 hrs. Measures are described further in **Table 8** below.

6.C.3. ***Symptom Assessment***. To obtain patient self-reports of symptoms, we approached patients twice weekly using the Condensed Form of the Memorial Symptom Assessment Scale (MSAS-C),[65] which is now being used for symptom assessment in the Candidate's ongoing R01 project. The MSAS-C asks about distress

from nine physical symptoms and frequency of three psychological symptoms; association of these symptom characteristics with quality of life and survival formed the basis for derivation of the MSAS-C from the original, longer, Memorial Symptom Assessment Scale.[66] Patients rated distress from physical symptoms on a 5-point verbal descriptor scale: "not at all," " a little bit," "somewhat," "quite a bit," "very much." For psychological symptoms, frequency was rated on a 4-point scale: "rarely," "occasionally," "frequently," "almost constantly." During preliminary data collection, we also assessed three additional physical symptoms (unsatisfied hunger, unsatisfied thirst, and inability to communicate) and we asked patients separately about dyspnea during full ventilatory support and during weaning from mechanical ventilation, whereas the original MSAS-C contains a single dyspnea assessment.

6.C.4. ***Symptom Reports***. Seventy-two percent (36/50) of patients were able to self-report symptoms on at least one occasion during the period of RCU treatment and, among these, 89% provided symptom reports more than once. The average number of symptom reports for the group of patients giving reports was 3.6 (95% CI of 2.9 - 4.3) over an average of 3 to 4 weeks under treatment in the RCU. Reasons for failure to obtain responses to approaches for symptom assessment were as follows: the patient lacked capacity (98 of 172 unsuccessful approaches, 57%), the patient refused to answer (33/172, 19%), other reasons (e.g., the patient was asleep, off the unit for a test, etc.) (41/172, 24%). There was no significant difference between patients providing symptom self-reports ("responders") and those not providing such reports ("nonresponders") in age, gender, ethnicity, source ICU, or baseline functional status. Nonresponders had significantly higher APACHE II scores at study entry (mean of 22.8, 95% CI of 21.2 – 24.3 for nonresponders versus mean of 19.2, 95% CI of 17.4 – 20.9 for responders, P = 0.003).

Figure 1.

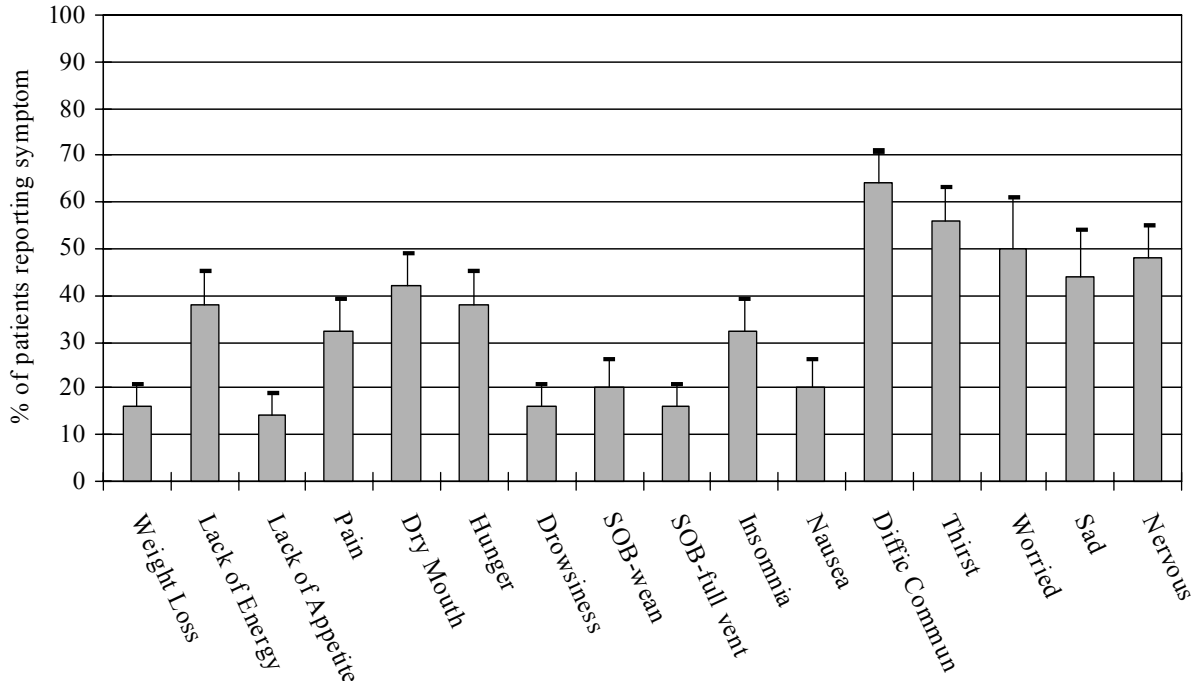


Figure 1. **Prevalence of Symptoms at Highest Levels of Severity (N = 50)**. The figure shows the percent of study patients (including patients not providing symptom reports as well as those reporting symptoms) reporting at least one symptom episode at the 2 highest levels of the physical and psychological symptom scales of the Condensed Form of the Memorial Symptom Assessment Scale (further details in the text, Section 6.C.4.). Error bars represent standard error of the mean. SOB-wean = shortness of breath during weaning from mechanical ventilation; SOB-full vent = shortness of breath during full ventilator support; Diffic Commun = difficulty in communicating.

Among patients responding to symptom assessment, all except one were symptomatic. Mean number of symptoms experienced by these patients at each assessment was 8.6 (95% CI of 7.9 – 9.4). Thirteen of 15 symptoms (including pain, dyspnea, unsatisfied hunger and thirst, and sadness) were found in at least half of the preliminary cohort of 50 patients and all symptoms were found in over one-third of these patients. As shown in **Figure 1** above, among the 50 patients, prevalence of symptoms at the highest levels of severity ("quite a bit" and "very much" distress for physical symptoms, "frequently" and "almost constantly" for psychological symptoms) ranged from approximately 50% for unsatisfied thirst, worry, and nervousness to 15% for

drowsiness. One-third of patients reported severe pain. One in five patients experienced severe dyspnea. Forty to 50% of patients reported severe psychological symptoms (sadness, nervousness, worry) and over 60% of patients reported severe distress due to difficulty communicating.

Using the MSAS scoring system,[66] we calculated scores of symptom severity for individual symptoms, subscales of physical and of psychological symptoms, and overall symptom distress (encompassing all symptoms) (**Table 5**). Physical symptoms were scored for distress from 0.8, "not at all," to 4.0, "very much;" psychological symptoms were scored for frequency from 1.0, "rarely" to 4, "almost constantly." Among patients reporting symptoms as present, the mean score for overall symptom distress was 2.60 (range 1.60 to 3.42); mean scores for the physical and psychological subscales were 2.56 and 2.77 (ranges 1.60 to 3.31 and 1.25 to 4.00) respectively (**Table 5**). Individual symptom scores are in **Table 5.**

Table 5.
Symptom Severity (Distress/Frequency) for Patients Reporting Symptom as Present

Symptom	N	Mean Severity (95% C.I.)	Worst Severity (95% C.I.)
		(**Scale is 0.8 – 4.0**)	
Pain	23	3.02 (2.67 – 3.36)	3.27 (2.91 – 3.63)
Unsatisfied thirst	32	3.09 (2.83 – 3.36)	3.53 (3.24 – 3.81)
Dry mouth	26	2.87 (2.50 – 3.24)	3.42 (3.08 – 3.75)
Difficulty sleeping	23	2.84 (2.47 – 3.20)	3.13 (2.71 – 3.55)
Nausea	19	2.75 (2.27 – 3.23)	2.91 (2.40 – 3.41)
Unsatisfied hunger	26	2.75 (2.38 – 3.11)	3.11 (2.75 – 3.47)
Lack of appetite	23	1.52 (1.11 – 1.92)	1.81 (1.28 – 2.33)
Shortness of breath (during weaning)	22	2.40 (1.96 – 2.85)	2.58 (2.07 – 3.09)
Shortness of breath (full vent. support)	24	1.63 (1.19 – 2.06)	2.03 (1.44 – 2.62)
Lack of energy	31	2.45 (2.04 – 2.86)	2.84 (2.42 – 3.26)
Feeling drowsy	30	1.43 (1.08 – 1.79)	1.84 (1.37 – 2.31)
Weight loss	28	1.48 (1.08 – 1.88)	1.69 (1.21 – 2.16)
Difficulty communicating	35	3.46 (3.17 – 3.76)	3.70 (3.41 – 3.99)
Sad	30	2.78 (2.46 – 3.10)	3.10 (2.77 – 3.43)
Worried	31	2.81 (2.49 – 3.13)	3.29 (2.97 – 3.61)
Nervous	31	2.67 (2.36 – 2.98)	3.16 (2.85 – 3.48)
Symptom Subscales:			
Physical Symptoms	36	2.56 (2.41 – 2.71)	2.82 (2.66 – 2.98)
Psychological Symptoms	33	2.77 (2.52 – 3.02)	3.20 (2.94 – 3.45)
Overall Symptom Distress	36	2.60 (2.44 – 2.76)	2.89 (2.73 – 3.05)

We scored responses using the Memorial Symptom Assessment Scale scoring system of Portenoy et al.,[66] as described in the text. **Mean Severity** = overall mean of mean levels of distress (for physical symptoms) and frequency (for psychological symptoms) for the individual responding patients. **Worst Severity** = overall mean of worst (highest) levels of distress and frequency reported by individual responders. The Physical Symptom and Psychological Symptom Subscale scores were calculated as the mean of the individual physical symptom and psychological symptom scores, respectively. The Overall Symptom Distress score was the mean of all individual symptom scores.

6.C.5. ***Other Outcomes.*** As shown in **Table 6** below, half of the patients were successfully liberated from mechanical ventilation. However, few returned to the community, where most had been living with acceptable functionality before the hospitalization. Most hospital survivors were discharged to skilled nursing facilities; only 2 among our cohort of 50 went home from the hospital. Although 42/50 (84%) were alive at hospital discharge, more than half of the cohort was dead at three-month post-discharge follow-up. Of survivors, 32% were dependent in all activities of daily living (ADLs) at 3 months and 33% were dependent in all ADLs at 6 months. Mean scores on the motor domain of the Functional Independence Measure[68] (FIM-Motor) (7-point scale from 1 - total assistance to 7 - complete independence for each of 13 motor items, summed to range from 13 - completely dependent to 91 - completely independent) decreased from 75.2 on admission (range 13 to 91) to 46.1 (range 13 to 91) at 3 months and 57.4 (range 13 to 91) at 6 months after RCU discharge.

Table 6. Outcomes of Chronically Critically Ill Study Patients (N=50)

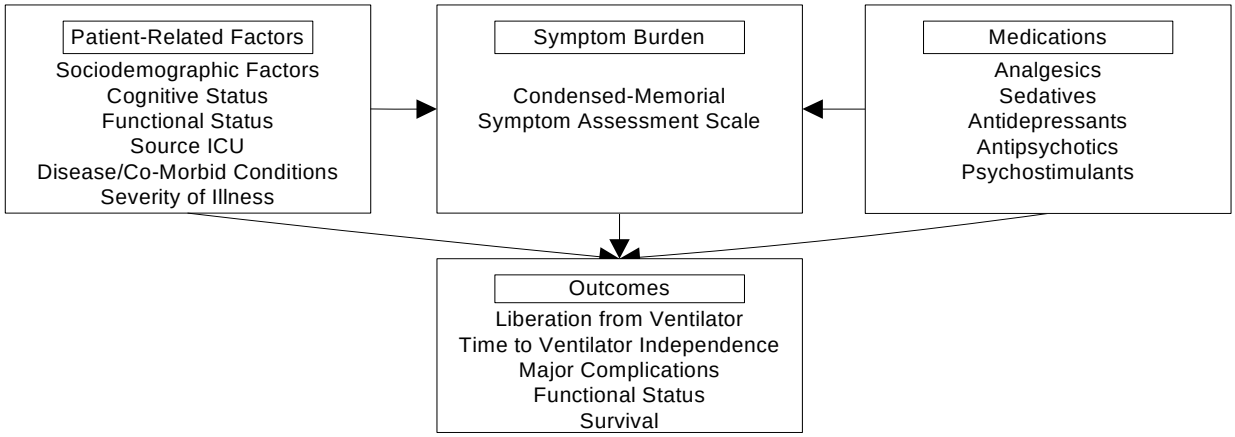
Length of Stay, median (range) no. days	
RCU	25.5 (8-76)
Hospital	55.5 (19-135)
Liberated from Mechanical Ventilation, no. (%)	25 (50)[a]
Time to Ventilator Liberation, median (range) no. days	12 (4-33)[a]
Hospital Discharge Site, no. (%)	
Home	2 (4)
Skilled Nursing Facility	23 (46)
Rehabilitation Facility	12 (24)
Other	5 (10)
(Died in hospital)	8 (16)
Cumulative Mortality, no. (%)	
RCU	6 (12)
Hospital	8 (16)
Three Months After RCU Discharge	26 (52)
Six Months After RCU Discharge	30 (60)
Functional Independence Measure (Motor) Score,[68] mean ± S.D	
RCU Discharge	18.0 ± 11.9[b]
Three Months after RCU Discharge	46.1 ± 30.5[c]
Six Months after RCU Discharge	57.4 ± 34.4[d]

[a]Excludes patients who died in the RCU. [b]N = 43: 6 patients died in the RCU, 1 withdrew from study participation at RCU discharge. [c]N = 22: 26 patients died and 2 patients withdrew before 3 month follow-up. [d]N = 18: 30 patients died and 2 patients withdrew before 6 month follow-up.

6.D. Research Design and Methods

6.D.1. ***Overview of Current R01 Project***. The Candidate's current R01 project is a prospective cohort study of the self-reported symptom experience of patients under treatment for chronic critical illness in Mount Sinai's Respiratory Care Unit. **We hypothesize that distressing physical and psychological symptoms are common among chronically critically ill patients and are associated with an increased risk of adverse clinical and utilization outcomes**. To test these hypotheses, we assess the prevalence and characteristics of symptoms as self-reported in real time by chronically critically ill patients throughout the period of treatment in our RCU. We also prospectively collect data with respect to selected patient-related and care process variables that have previously been associated with outcomes of mechanical ventilation and with functional status and survival of acutely and chronically critically ill patients. We will then systematically evaluate the association of symptom burden with important outcomes of chronic critical illness, including as our **primary outcomes**: success in liberation from mechanical ventilation, time to ventilator independence, and occurrence of major medical/surgical complications during RCU treatment; and, as **secondary outcomes**, vital and functional status at RCU discharge, and survival and functional status in the early post-discharge period. Our conceptual model is shown in **Figure 2** below. The project was approved by our Institutional Review Board and is funded by an R01 grant from NIA for the period May 2003-April 2007.

Figure 2. Conceptual Model



6.D.2. ***Study Population/Recruitment***. Eligibility is established by elective tracheotomy and transfer of the patient from an adult ICU to the RCU for weaning from mechanical ventilation.[9,25] Elective tracheotomy reflects the clinical impression that the patient is neither expected to be liberated from the ventilator nor to die in the immediate future, and therefore serves as a practical point of demarcation between acute and chronic critical illness. We exclude patients with a prior history of ventilator dependence or RCU admission, and those without sufficient English proficiency to understand and respond to the study instruments. Recruitment to date has kept pace with our expectations, based on preliminary data, that we will enter approximately 150 study subjects each year, for a total of 450 during the study period (patient recruitment continues for 36 months). Approximately 2/3 of these subjects are expected to provide self-reports of symptoms, yielding approximately 300 symptom assessment respondents over the period of the study.

Table 7. Study Variables (Other Than Symptom Assessments)

VARIABLES		DATA SOURCE	VARIABLES		DATA SOURCE
PATIENT-RELATED VARIABLES			MEDICATIONS		
Sociodemographic Factors	Age Gender Race Residence	MR, I/V	**Medication Type**	Analgesic Sedative Antidepress./Psychostim. Antipsychotic	MR, DB
Cognitive Status	Dementia history APACHE III-APS OMCT CAM-ICU Duration of delirium	MR, I/V	**Medication Dose**	Opioids – morphine equivalents	MR, DB
Functional Status	FIM–Motor FIM–Motor subscales Pre-hosp. independence	I/V	**Medication Frequency**	Number of medication days Medication/ventilator days Medication/RCU days	MR, DB
Source ICU		MR	OUTCOMES		
Disease Processes/ Co-Morbid Conditions	Admit./respir. failure diagnoses Chronic co-morbidities Charlson Index Acute co-morbidities Med./surg. complications	MR, I/V	**Liberation from ventilator**		MR
			Time to ventilator indep.		MR
			Med./surg. complications		MR, I/V
			Functional status		I/V
Severity of Illness	APACHE III-APS Lab Parameters	MR, DB	**Survival**		MR, I/V, DB

Data sources are: medical record abstraction (MR); interviews of patients, surrogates and staff (I/V); and existing databases (DB). APACHE III-APS = Acute Physiologic Score of APACHE III severity of illness scoring system;[74] CAM-ICU = Confusion Assessment Method for the Intensive Care Unit;[75,76] Charlson Index = Charlson Co-Morbidity Index[71] score; FIM-Motor = Motor Domain of the Functional Independence Measure;[68] OMCT = Six-Item Orientation-Memory-Concentration Test.[69] Further description of study measures is in **Table 8** below.

6.D.3. ***Patient Management***. Patient care in the RCU is standardized through consistent application of detailed, comprehensive clinical protocols including a flow-charted algorithm for weaning and an interdisciplinary care map covering multiple other aspects of care.[11] In accordance with these protocols, treatment of RCU patients proceeds under the direction of the patients' primary attending physicians and responsible nurse practitioners, in consultation with attending physicians in pulmonary and critical care medicine, as described above (Section 6.C.1.). Attending physicians conduct daily patient rounds with the nurse practitioners, formulating a care plan for each patient. In accordance with this plan, nurse practitioners in continuous attendance on the RCU coordinate patient management and discharge.

6.D.4. ***Data Collection***. **This section describes our independent and dependent study variables**. Our **independent variables** consist of symptom data and other sets of variables that have previously been shown to be determinants of outcomes in critical illness.[72,73] **Primary dependent variables** for this study are: liberation from mechanical ventilation, time to ventilator independence, and the occurrence of medical or surgical complications in the RCU. **Secondary dependent variables** include survival and functional status at RCU discharge and at 3 and 6 months following RCU discharge.

Table 7 above lists the independent and dependent variables and the data sources: abstraction of medical records (MR); interviews of patients, surrogates, nursing staff, nurse practitioners, and/or physicians (I/V); and existing databases (DB). As prescribed by a detailed study manual, a research nurse who has been appropriately trained, certified, and evaluated collects data on a data collection instrument, from which it is entered into an Access database constructed for this project.

6.D.4.1. *Definitions/Measures for Independent Variables*. **Table 8** summarizes definitions and measures for specific independent variables of interest (other than symptom assessments). These data are collected at study entry unless otherwise specified in the table.

Table 8: Definitions/Measures for Independent Variables

- **Diagnostic information (admission and respiratory failure diagnoses)**: Classified in categories adapted from APACHE III prognostic system[74] for critically ill hospitalized adults. Because diagnoses and co-morbid conditions (as defined below) may be difficult to interpret from medical records, records are "over-read" for those variables by a physician-investigator.
- **Chronic co-morbid conditions**: Specified conditions known to be present at hospital admission or up to 6 weeks before RCU admission.[17,77] Data with respect to chronic co-morbid conditions is used to calculate the **Charlson Co-Morbidity Index**[71] score.
- **Acute co-morbidities**: Specified conditions occurring within 6 weeks before admission to the RCU.[17]
- **Functional status**: Assessed using the **motor domain** of the **Functional Independence Measure** (FIM-Motor)[68] and FIM-Motor subscales. For these physical items, strong correlation has been shown between information from surrogates and information from patients themselves, and also between responses to in-person interviews and telephone interviews.[78-82] We measure functional status (retrospectively) at hospital admission and (prospectively) at study entry, RCU discharge, and 3 and 6 months post-discharge.
- **Cognitive status**: Measures include **history of dementia** as reflected in medical record and reported by surrogates; **Six-Item Orientation-Memory-Concentration Test**[69](OMCT) (intact cognition defined as score $\leq$ 10 on this measure), and the **Confusion Assessment Method for the ICU**[75,76] (CAM-ICU) for delirium evaluation. All measures are collected at study entry, OMCT and CAM-ICU are also administered at symptom assessments; CAM-ICU is administered by telephone at post-discharge follow-up.[83]
- **Laboratory/respiratory parameters**: Physiologic derangements and nutritional status assessed by laboratory/respiratory variables that have been associated with outcomes of interest here in previous studies of critically ill patients.[17,18,32,84-86] An accepted measure of illness severity in predicting outcomes of critical illness, **Acute Physiologic Score** (APS) is calculated using the APACHE III formula[74] and physiologic data during the first 24 hours after RCU admission.[17,84,87]
- **Major medical/surgical complications during RCU stay**: Data collected prospectively and classified in same categories as acute co-morbidities.
- **Sedative, analgesic, antidepressant, antipsychotic, and psychostimulant medications**: Data collected prospectively throughout RCU stay.

6.D.4.2. *Symptom Assessment Instrument*. Our symptom assessment instrument is the Condensed Form of the Memorial Symptom Assessment Scale (MSAS-C),[66] which we used this instrument successfully in our preliminary data collection (Section 6.C. above). The MSAS-C as modified for our use encompasses 12 physical symptoms (with separate assessment of dyspnea during full ventilator support and during weaning) and 3 psychological symptoms. As above (Section 6.C.2.), patients rate distress from physical symptoms on a 5-point verbal descriptor scale ("not at all" to "very much" distressed), and frequency of psychological symptoms on a 4-point scale ("rarely" to "almost constantly"). The validity and reliability of this instrument have been well established.[66,67]

6.D.4.3. *Symptom Assessment Protocol*. We use the MSAS-C to obtain self-reports of symptoms in "real time" twice during each week (Monday-Thursday or Tuesday-Friday) of the RCU stay. Given that the average length of RCU stay is 3-4 weeks, patients are approached on average 6-8 times for symptom assessment. The research nurse seeks symptom responses from all study patients who can respond to the scale and agree to do so, regardless of their cognitive status.[88,89] Recognizing, however, that both dementia and delirium may affect these responses, we use the Six-Item Orientation-Memory Concentration Test (OMCT)[69] (cognitive impairment defined as score > 10 on this measure) and the ICU Adaptation of the Confusion Assessment Method (CAM-ICU)[75,76] to assess cognition at the time of symptom assessment. These data will be utilized in subsequent analyses to examine the possible impact of cognitive impairment on symptom responses. To minimize the potential effect of dementia and delirium on ability to accurately recall, integrate, and report symptoms over time, we focus our symptom assessments on the patient's experience during the previous 24 hours rather than a longer period. Reasons for failure to obtain responses are recorded.

6.D.4.4. *Outcome Variables*. Our primary outcomes/dependent variables are as follows: **success in liberation from mechanical ventilation,** defined as 168 hours of unassisted breathing, regardless of whether the patient subsequently requires mechanical ventilation;[84] **time to ventilator independence**, defined as the number of days from RCU admission to the first day of the period demonstrating liberation; and **occurrence of major medical and surgical complications,** which were specified a priori. **Survival**, a secondary outcome, is determined at discharge from the RCU and hospital, and by telephone contact after 3 and 6 months for patients discharged alive from the RCU. As in **Table 8** above, **functional status**, another secondary outcome, is assessed using the motor domain of the Functional Independence Measure at RCU discharge and (by telephone) at 3 and 6 months after discharge. We have been highly successful in obtaining post-discharge follow-up data for our RCU research subjects.

6.D.5. *Data Analysis*. Patient recruitment will continue until month 39 (July 2006), with completion of data collection including post-discharge contacts by month 45 (January 2007). We then plan to conduct our main analyses, including descriptive analyses and statistical modeling, as set forth below.

6.D.5.1. *Considerations for Data Analysis*. This section summarizes our approach to missing data, to symptom responses provided during episodes of cognitive impairment, to internal consistency of responses to our modified symptom assessment instrument, and to evaluation of data quality control.

6.D.5.1.1. *Missing Data*. To evaluate for the possibility of systematic bias, we will compare demographic and health characteristics of patients who provided no symptom reports with those of patients who responded to at least one approach for symptom assessment, and to those of patients who provide responses to ≥ 50% of approaches. Based on our preliminary data, we expect minimal missing data about survival or about functional status of survivors. We recognize that post-discharge data about functional status will be limited by the mortality rates at those time-points. To address this limitation, we will explore assignment of the lowest FIM-Motor score (i.e. 13, completely dependent) to patients dying before the post-discharge functional assessment. As another approach, we will limit consideration to survivors, recognizing that inferences about associations between symptom burden and post-discharge functional status would then be limited to this group.

6.D.5.1.2. *Possible Effects of Cognitive Impairment on Symptom Responses*. Although prior research suggests that self-reports of symptoms from patients with cognitive impairment are as valid as those of cognitively intact patients if the patient can complete the scale,[88,89] we will explore in several ways whether responses obtained during periods of cognitive impairment differ systematically from those obtained when subjects are not cognitively impaired. Our analyses will include: comparison of the amount of missing data within each assessment for cognitively intact and cognitively impaired episodes of measurement; for

assessments obtained during cognitive impairment, examination of the extent to which subjects gave the same response for multiple symptom items; and comparison of the (adjusted) mean of scores of symptoms reported during episodes of cognitive impairment with the (adjusted) mean of those during episodes of intact cognition. These analyses will be performed in the context of repeated measures Analysis of Variance with estimates based on Generalized Estimating Equations methodology, and include a patient and a time effect, with the latter based on linear and quadratic terms.

6.D.5.1.3. *Internal Consistency of Symptom Assessments*. We will perform a factor analysis (principal component analysis with varimax rotation) of the symptom items in the original MSAS-C and the additional items we incorporated. We anticipate that two of the new items, unsatisfied thirst and unsatisfied hunger, will load with the original list of physical symptoms, and that inability to communicate will load with the original list of psychological symptoms. Internal consistency of an overall symptom distress scale (all items) and physical and psychological symptom distress subscales will be assessed using Cronbach's alpha. If the added items load as we anticipate in the factor analyses and the new scales display acceptable internal consistency, we will include them in the appropriate scales for purposes of further analyses using these scales. If they behave differently, we will restrict further analyses using these scales to the original items, and analyze the new items separately.

6.D.5.1.4. *Evaluation of Data Quality*. We will use the kappa statistic to compare the data abstracted from medical records by two independent raters as to all study variables for a random sample of 10% of patients enrolled in the study. In addition, we will examine data validity by determining the sensitivity and specificity of diagnoses and co-morbid medical conditions coded by the research nurse as compared with those of the physician who "over-reads" these diagnoses and conditions during the regular data collection.

6.D.5.2. *Descriptive Analyses.* We will conduct **descriptive analyses** of data relating to characteristics of the patients, to care processes, symptom experience, and our outcomes/dependent variables.

6.D.5.2.1. *Symptom Experience*. Our main independent variable is symptom experience. To summarize symptom prevalence, we will use several approaches, including: calculation of the percentage of patients reporting each individual symptom as present; calculation of the mean and median number of symptoms experienced by patients; and determination of the ratio of the number of affirmative responses for each symptom item to the total number of occasions on which patients provided symptom responses for that item. To identify possible changes and patterns in the experience of symptoms over time, we will also describe symptom prevalence during specific time periods after RCU admission. Analyses of symptom intensity will include determination of the number of responses for each physical symptom at each level of distress, and the number of psychological symptom responses at each level of frequency. Using the MSAS scoring system[71] we will calculate mean and maximum scores for each symptom in our assessment instrument, for overall symptom distress (the average of the scores for all of the symptoms) and for physical and psychological symptom subscales (sum of the scores of the individual physical or psychological symptoms divided by the number of such symptoms). From these values, we will compute the means for the group as a whole of the mean and maximum symptom scores.

6.D.5.2.2. *Outcomes/Dependent Variable Description*. We will determine the rate of successful liberation from the ventilator, including in and then excluding from the denominator patients who were mechanically ventilated until death in the RCU. We will also tabulate frequency distributions for liberation within selected time periods. We will calculate the number of patients developing at least one major medical/surgical complication in the RCU. We will then determine the number of patients with multiple complications, compute central tendency measures for the number of complications, and tabulate frequency distributions for each of these complications. Mortality rates at RCU discharge and our post-discharge time points will be calculated. Mean/median scores on the motor domain of the FIM will be determined for each time point of administration.

6.D.5.3. *Model Building*. We will perform **statistical modeling** to test the hypothesis that symptom burden is associated with adverse clinical and utilization outcomes of chronic critical illness. The independent variable of primary interest is symptom burden. Covariates are variables listed in **Table 7**. Our **primary analyses** will focus on **three outcomes**: **overall success in liberation from the ventilator** (multiple logistic regression); **time to successful ventilator liberation** (Cox proportional hazards modeling, using time-dependent covariates including symptom measures); and the development of **major medical/surgical complications in the RCU**

(multivariate logistic regression of dichotomous outcome variable; Poisson regression if the number of complications is well fit).

We will also explore the association of symptom burden with several **secondary outcomes**: **survival** to RCU discharge and 3 and 6 months post-discharge (Cox proportional hazards models) and **functional status** at the same time points (ordinary least squares regression). We will incorporate in our modeling appropriate strategies to address missing values (e.g., analyzing both the individual, bi-weekly symptom scores and summary measures of these scores, including adjusted mean symptom scores, the rate of change in these scores, and either a quadratic trend, a measure of variability of the symptom, or the maximum scores).

All analyses will include certain critical variables that have been associated with our outcomes of interest in prior studies. To select additional variables, we will first use univariate statistics to explore the association between each of the individual, independent variables and outcome variables. Next, we will enter into the regression equation all variables that are associated with the dependent variable at a significance level of $P < 0.15$. If there are no variables within one or more of the sets of variables defined in **Table 7** that meet this criterion, we will enter one or more variables from the missing set(s) based upon a priori clinical relevance. Conventional analysis of residuals and tests of model specification will be applied and transformations of variables made, if necessary, to ensure that the model is well specified. Discrimination and calibration of the logistic regression models used to test the hypotheses about dichotomous outcomes will be assessed by calculating the area under the receiver operating characteristics curves and the Hosmer-Lemeshow statistic. Fit of the proportional hazards models for survival outcomes will be appraised by analysis of residuals. For the linear regression models, fit will be measured using adjusted R^2 and root mean squared error.

Finally, to take account of potential systematic differences between symptom responses given during periods of cognitive impairment (OMCT > 10) and those given when cognition was intact (OMCT ≤ 10) (see Section 6.D.4.3.), we will construct two series of models: 1) using in the measures of symptom burden only the responses given during periods of intact cognition, and 2) using all responses regardless of cognitive status. We will compare parameter estimates for these two sets of models.

6.D.6. ***Power Calculations***. Based on experience to date, we expect approximately 175 admissions annually to the RCU, of whom 150 will be eligible for and consent to study participation. Approximately 2/3 of these patients will provide symptom reports, for a total of approximately 300 patients reporting symptoms during the 36 months of patient recruitment. Although we plan as above to explore various measures of our main predictor variable, symptom burden, we based our power calculations on dichotomization of study subjects into groups of approximately 150 subjects above and below the median score for overall symptom distress. We will have 80% power to detect a difference of 49% versus 65% in the rate of successful liberation from the ventilator, using a 0.05 significance level with a two-tailed test. (Since we will be evaluating time to ventilator independence, we will actually be able to detect a smaller difference.) We will also have 80% power to detect a difference of 77% vs. 62% in the occurrence of at least one major medical/surgical complication during the period of RCU treatment, again using a 0.05 significance level and a two-tailed test. For survival outcomes, we can detect a difference of 34% versus 50% in mortality at 6 months after discharge.

6.D.7. ***Current Status of Project and Time Line for Completion.***

The Candidate's R01 project started May 1, 2003. As provided in the original Work Plan/Time Line for that project, we have completed our data collection instrument and a detailed study manual, and constructed a database for this project. We have also trained our research nurse in use of our symptom assessment instrument and collection and entry of other data. Patient recruitment has now begun, and will continue to month 39 (July 2006). Data cleaning will commence in month 12 (April 2004). We will start preliminary analyses in month 24 (April 2005), and expect to complete preliminary analyses for our primary outcomes by month 36 (April 2006). During month 45 (January 2007), we will complete post-discharge contacts and further data cleaning. We plan to conduct further analyses beginning in month 36, and to complete analyses and prepare reports from months 42-48 (October 2006-April 2007). As described below, emerging results from this project will serve as a basis for the next phase of Dr. Nelson's research program and career.

6.D.8. ***Further Research Building on the Current R01: Interventions to Improve Palliative Care of Older Adults with Chronic Critical Illness***. The Candidate's recently-funded R01 project will yield new information

about the symptom experience of older adults with chronic critical illness and about associations between symptom burden and other clinical and utilization outcomes. For the first time, these data will provide a solid evidentiary foundation for development of interventions to improve symptom experience and other associated outcomes of chronically critically ill patients. The Candidate plans to use the observational data and the research time protected by the K02 award to embark on a program of interventional investigation that will extend logically from her current R01 project and will advance her career from newly independent investigator to research leader. In this next phase of research, the Candidate will test the **hypothesis** that **treatment alleviating symptom distress will be associated with favorable clinical and utilization outcomes of chronic critical illness** including 1) greater patient comfort; 2) a higher rate of success in liberation from mechanical ventilation; and 3) a shorter time to ventilator independence. With protected time permitted by the K02 award, Dr. Nelson will conduct pilot interventional studies building on the current research and then incorporate the emerging results of the R01 and pilot studies in applications for further R01 or comparable funding for full-scale randomized, controlled trials of interventions to improve important aspects of palliative care for older adults with chronic critical illness. At the present stage of the observational research, it is premature to finalize protocols for interventional studies. However, a proposed pilot interventional study is described below to illustrate the transition from observational to interventional research that the Candidate plans for the K02 period. Dr. Sean Morrison, who has been her research mentor and senior collaborator, will support the costs of Dr. Nelson's pilot research with funds earmarked for that purpose in the K24 Mid-Career Investigator Award in Patient-Oriented Research (#1 K24 AG022345-01) that he recently received from NIA. Protocols for pilot research, including the study summarized below, will be presented to our Institutional Review Board when the protocol is finalized; in addition, any subsequent application for funding for a full-scale interventional trial will include all information required for research involving human subjects.

6.D.8.1. *Proposed Pilot Study of Nebulized Fentanyl as "Pre-emptive" Treatment for Dyspnea During Weaning of Chronically Critically Ill Patients from Mechanical Ventilation: Specific Aims*. As discussed in Section 6.C. above, the Candidate's preliminary data indicate that multiple physical and psychological symptoms are prevalent at high levels of intensity during chronic critical illness. Statistical modeling under Aim 2 of the recently funded R01 project is expected to identify distressing symptoms that are associated with other adverse clinical and utilization outcomes, which can then be targeted by an intervention intended both to reduce symptom distress and to improve associated outcomes. One example is a randomized, controlled trial, to be conducted initially as a pilot study, of "pre-emptive" treatment of dyspnea during weaning of chronically critically ill patients from mechanical ventilation. For the proposed pilot study, we would evaluate the use of nebulized fentanyl, as discussed more fully below. **Specific Aims** of this pilot study are: **1) to evaluate the feasibility, effect, and optimal dose of nebulized fentanyl as "pre-emptive" treatment for dyspnea during weaning of chronically ill patients from mechanical ventilation**; and **2) to evaluate adverse effects of nebulized fentanyl** in this clinical context.

6.D.8.1.1. *Dyspnea as a Target Symptom: Rationale*. As in Sec.6.C.4. above, half of the patients in Dr. Nelson's preliminary data collection experienced dyspnea, which was reported by these patients during full ventilatory support as well as during weaning from mechanical ventilation. While other symptoms may also be highly prevalent, dyspnea is attractive as a target symptom for interventional study because treatment may not only alleviate symptom distress but also facilitate weaning of chronically critically ill patients from mechanical ventilation. Dyspnea results from "efferent-afferent mismatch," that is, from a disassociation between central respiratory motor (efferent) activity and incoming (afferent) information from receptors in the airways, lungs, and chest wall structures.[90] Factors including fatigue and weakness of respiratory muscles, which necessitate a greater motor command to achieve a given tension in those muscles, serve to intensify the sensation of dyspnea. These same factors are critically limiting in the process of liberation from mechanical ventilation, particularly for older patients whose cardiovascular reserve is often reduced.[91,92] By reducing respiratory rate, force generation, and tissue oxygen consumption, treatment with an opioid would reduce respiratory muscle fatigue and thereby provide a physiologic advantage as well as symptom relief during liberation from mechanical ventilation.[93] Although we anticipate that dyspnea will be an appropriate target for the initial interventional research, the focus of the pilot could be shifted to another symptom if that appears more appropriate in light of emerging findings and analyses of the ongoing R01 study. We expect that treatment of psychological symptoms will also warrant intensive further investigation as these symptoms are common and severe during chronic critical illness and successful treatment may be associated with other favorable outcomes for chronically critically ill patients.[61,62]

6.D.8.1.2. *Opioid as Treatment for Dyspnea: Rationale*. The most widely used and extensively studied pharmacologic agents for treatment of dyspnea are opioids.[94] In this context, opioids are believed to act by multiple mechanisms including decrease in central respiratory responsiveness to CO_2.[93] Opioids may also act centrally by altering perception of dyspnea and peripherally on opioid receptors in the lung without affecting respiratory drive.[93,95] In addition, opioids may relieve dyspnea by reducing O_2 consumption and improving cardiovascular function.[94] Existing evidence indicates that opioids are effective in alleviating dypnea and more effective than other medications in this respect; only opioids were effective in controlled studies.[94] However, there are no studies of opioid (or other) treatment of dyspnea during chronic critical illness, although dyspnea is a common and important limiting factor in the process of liberation from mechanical ventilation. In addition, potential adverse effects of opioids, including respiratory depression, hypotension, sedation, and constipation, are relevant in this clinical setting. It would be reasonable, therefore, to undertake a randomized, controlled trial of opioid administration as "pre-emptive" treatment for dyspnea during weaning of chronically critically ill patients from mechanical ventilation.

6.D.8.1.3. *Nebulized Fentanyl as the Study Opioid Drug*: *Rationale*. Opioid receptors are abundant in the airways and activation of pulmonary-irritant receptors and C-fibers, which appear to be involved in mediation of dyspnea, is inhibited by opioids in animal models.[95a] On this theoretical basis, small studies of nebulized morphine for dyspnea have been conducted with inconsistent and generally negative results.[94] Recently, however, successful treatment of dyspnea using nebulized fentanyl, which is a potent synthetic opioid, has been reported in cancer patients.[96,97] Inhaled fentanyl has several potential pharmacologic advantages as compared with inhaled morphine. Fentanyl is highly lipophilic, which is thought to facilitate more rapid absorption in the airway, while there is less histamine release and therefore less bronchospasm in association with fentanyl.[93,98] In a recent study, O2 saturation increased and respiratory rate decreased within five minutes of administration of nebulized fentanyl and these effects were sustained for at least one hour;[96] the analgesic effect of nebulized fentanyl continued for at least two hours in another study.[99] Although there is more experience with intravenous or oral opioid treatment for dyspnea, administration by nebulizer for inhalation is likely to be more acceptable to study patients than an intravenous medication and, even with tracheotomy, many mechanically ventilated patients cannot swallow oral medication safely or reliably; nebulization may deliver fentanyl more quickly than oral transmucosal formulations. Administration by nebulization may also cause fewer adverse effects because most of the drug is not is systemically absorbed.[99] Fentanyl citrate is widely available, readily nebulized and inexpensive. The only known contraindication to nebulized fentanyl is allergy to fentanyl, which is rare. For these reasons, nebulized fentanyl warrants evaluation as the study drug in this pilot trial.

6.D.8.1.4. *Preliminary Protocol for Proposed Pilot Study*. Subjects for the pilot study will be chronically critically ill patients as previously defined (i.e., with elective tracheotomy for failure to wean from mechanical ventilation in an adult ICU)[9](see Section 6.D.2. above) who are undergoing weaning in Mount Sinai's RCU, who can provide self-reports of dyspnea, and who provide informed consent for study participation. Weaning in the RCU is standardized by a flow-charted algorithm containing goals and thresholds for incremental lowering of support to the point of ventilator liberation. Patients initially receive trials of decreasing levels of pressure support ventilation; frequency and duration of these trials is increased as tolerated. Trials of increasing time on a tracheostomy mask (i.e. oxygen supplementation via collar mask placed over the tracheostomy tube, without mechanical ventilation) are then given, until the patient is able to breathe without mechanical ventilation throughout the day and night, using only oxygen supplementation via the collar. To maximize homogeneity in the study group, patients will become eligible for study participation on the first day that a tracheostomy mask trial ("weaning trial") of at least 2 hours is planned. We will exclude patients who are already receiving opioid treatment for another indication and those with a past history of opioid abuse. Evidence of significant CO_2 retention at baseline (level $\geq$ 50 mm Hg on arterial blood gas or end-tidal (noninvasive) measurement of CO_2, or of cardiovascular instability (including systemic hypotension) will also be exclusion criteria. In this pilot study, we aim to enroll 7 to 10 patients in each of the 3 treatment blocks described below.

6.D.8.1.5. *Randomization***.** Using a computer-generated random number table, consenting patients will be randomized to one of 3 treatment blocks for this 3-day protocol. Injectable fentanyl citrate will be diluted with normal saline to form the solution for aerosolization. Block I will receive low dose nebulized fentanyl (25 micrograms) on day 1 followed by nebulized placebo (normal saline) on day 2 followed by nebulized high dose fentanyl citrate (50 micrograms) on day 3. Block II will receive placebo on day 1 followed by low dose fentanyl on day 2 followed by high dose fentanyl on day 3. Block III will receive low dose fentanyl followed by high dose fentanyl followed by placebo. Designing the experiment in this manner will allow us to better control

for a placebo effect while at the same time allowing us to obtain preliminary data about the optimal effective dose of nebulized fentanyl.

6.D.8.1.6. *Administration of Medication or Placebo*. Patients undergoing weaning in the RCU are given one or more trials of reduced ventilatory support each day, with the first such trial in the morning. For study patients scheduled to receive a weaning trial of at least two hours as routine clinical care, the morning weaning trial will be standardized for purposes of this research at a duration of two hours for 3 consecutive days, during which the pilot study will be conducted. Fifteen minutes prior to the commencement of each of these 3 trials, patients will receive high or low dose nebulized fentanyl citrate in normal saline or nebulized normal saline alone in a double-blind fashion. Administration will be over approximately 15 minutes using a Misty-Neb high-flow nebulizer (Allegiance Healthcare Corporation, McGaw Park, IL) attached to the tracheostomy tube; Patients will inhale the medication during tidal breathing, after which an Airlife tracheostomy mask (Allegiance) will be placed over the tracheostomy and the weaning trial will commence. Timing of administration of the study medication is based on existing evidence indicating that after inhalation of nebulized fentanyl, onset of analgesia occurs within approximately 15 minutes[100] and changes in respiratory parameters may occur earlier.[96] The low dose of fentanyl will be 25 ug in 2 ml of normal saline; the high dose of fentanyl will be 50 ug in 4 ml of normal saline; and the same volume of normal saline will be given to patients assigned to placebo treatment. These doses are based on a previous study of nebulized fentanyl for dyspnea in patients with advanced cancer,[96] on literature relating to nebulized fentanyl for analgesia,[100] and a review of current "best clinical practice" for use of nebulized drugs in palliative care.[98]

6.D.8.1.7. *Management of Opioid-Related Side Effects*. We will implement for both the intervention and placebo groups a protocol based on well-established guidelines for management of the following common opioid-related side effects:[101,102] constipation (docusate and senna, with or without enemas and/or lactulose for severe constipation), nausea (metaclopromide or prochloperazine), excessive sedation (methylphenidate), or delirium (olanzapine or risperdone or haloperidol). The protocol for side-effects management will be used for treatment, not prophylaxis; although prophylactic laxative treatment is generally recommended for patients receiving opioids, diarrhea is highly prevalent during chronic critical illness,[58] and we will therefore explore in this pilot study the initiation of the laxative protocol only after a 48-hour period without a bowel movement. Psychological dependence (addiction) is extremely rare even with extended use of opioids for medical purposes.[102] Patients may develop physical dependence, but this would not be expected to occur with such short-term administration as is provided in this protocol.[102]

6.D.8.1.8. *Data Collection*. Variables for pilot study will include: patient-related variables, clinical/physiologic variables, and utilization/process variables. Among patient-related variables, demographic and health (diagnoses and co-morbid conditions) information will be abstracted at study entry from medical records and existing hospital databases to characterize the patients participating in the study, to confirm the comparability of the treatment groups, and to provide a context for evaluation of the safety and effect of the intervention.

Clinical/physiologic variables will be measured at several time points during the protocol for administration of the study drug or placebo: Time 0 will be 15 minutes prior to nebulization, and Time I, Time II, Time III and Time IV will be 15 minutes, 30 minutes, 60 minutes and 120 minutes, respectively, after nebulization is completed (or when the patient is returned to full ventilator support, whichever is sooner). At each of these time points, we will obtain "real-time" assessments of dyspnea through patient self-reports. For this purpose, we plan to explore in the pilot trial use of a Visual Analogue Scale with anchors of "no shortness of breath" to "shortness of breath as bad as it can be" at the extremes.[90] If it is too difficult for these chronically critically ill patients to see or point to this scale, we will use a verbal descriptor scale such as the Borg Scale (a validated and reliable 10-point scale with verbal descriptors of intensity of breathlessness – "nothing at all" to "maximal" – anchored to specific numbers.)[103,104] The reliability and validity of these measures of dyspnea are well established.[90] In addition, we will collect at these time points physiologic parameters including the following: heart rate, blood pressure, respiratory rate, tidal volume, oxygen saturation (measured by co-oximetry), and end-tidal CO_2. At Time 0 (baseline) and immediately after the last time point (at the end of the weaning trial), we will determine negative inspiratory force and vital capacity as measures of respiratory muscle strength, fatigue, and respiratory drive.[105,106] Additional clinical variables: To identify potential adverse effects of opioid treatment for dyspnea, we will also prospectively collect on a daily basis clinical data with respect to bowel function (number of daily bowel movements reported by the patient's primary nurse), nausea (4 point scale,

none to severe), sedation (we will explore use of a 4-point scale adapted from Ferrell et al.[107] and of the 10-point Richmond Agitation and Sedation Scale[108]), and delirium (assessed by CAM-ICU[75,76]).

Utilization/process variables will include the proportion of individual weaning trials that proceed to completion, success in liberation from mechanical ventilation (defined as for the current R01 project, see Section 6.D.4.4. above), time to ventilator independence (number of days to the first day of the period demonstrating liberation), and lengths of stay in RCU and hospital.

6.D.8.1.9. *Data Analysis*. We will compare patient demographic and health information for the treatment groups to ensure effective randomization and comparability. We will use a GLM repeated measures analysis to compare mean ratings of dyspnea, oxygen saturation, respiratory rate, end-tidal CO_2, and other physiologic parameters for the three different treatment interventions (low dose fentanyl, high dose fentanyl, placebo) at each time point of measurement. To determine safety/adverse effects, we will also compare mean number of bowel movements each day, nausea and sedation ratings, and the frequency of delirium. The effect of the opioid intervention versus placebo will be explored with respect to success in and time to ventilator liberation, but we recognize that this pilot study is unlikely to have sufficient power to detect such differences. Emerging findings and analyses of the Candidate's ongoing R01 will be used to refine methods for this pilot study, which in turn will guide design of a full-scale randomized, controlled trial for which federal funding will be sought during the K02 period. If the pilot study indicates that nebulized fentanyl is safe and effective for treatment of dyspnea during weaning, the larger trial would be designed and powered to analyze the impact of relief of dyspnea on other clinical and utilization outcomes, such as success in and time to ventilator liberation.

6.D.8.10. *Summary*. In summary, this K02 Candidate has developed an independent program of investigation to inform and improve palliative care for older adults with chronic critical illness. This is a new field of aging research that the Candidate has helped to define and to which she brings a rare and valuable blend of expertise in critical care medicine and palliative medicine, a strong record of academic accomplishment, a network of productive collaborative relationships, and proven ability to obtain extramural research funding for her research program. Empirical evidence is urgently needed to guide efforts to alleviate suffering and improve other outcomes of chronically critically ill patients, who are a large and growing group of older adults with poor prospects for survival or functional recovery despite resource-intensive treatment. The Candidate is moving forward with research supported by the R01 award she recently received from NIA (her first NIH funding), which evaluates the symptom experience of chronically critically ill patients and examines associations between symptom burden and other clinical and utilization outcomes. In addition, she is already engaged in preliminary design of the next phase of research, which will use the observational findings and analyses of the current R01 project to develop and rigorously evaluate appropriate interventions to improve palliative care and associated outcomes for the chronically critically ill. The Candidate has reached an important juncture in her research career. To realize the full potential of her present RO1 study and future studies that will build on this pioneering project and her other research, she requires a sustained period of intensive focus on research and research-related activities, which in turn requires protection from clinical, teaching, and administrative responsibilities that currently compete for her attention. The Candidate will use this protected time, which is assured by the responsible leaders of her institution, to implement her detailed plan for research career development. By the end of the K02 award period, she will achieve each of the overall goals and specific aims described in this application, making a successful transition from newly independent investigator to leader of an internationally-recognized, strong and sustainable program of aging research.

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