# 424 R&R and PHS-398 Specific Table Of Contents

**SF 424 R&R Face Page**

1

**Table of Contents**

3

**Performance Sites**

5

**Research & Related Other Project Information**

6

- **Project Summary/Abstract (Description)**

7

- **Public Health Relevance Statement (Narrative attachment)**

8

- **Facilities & Other Resources**

9

**Research & Related Senior/Key Person**

13

- **Biographical Sketches for each listed Senior/Key Person**

19

**Research & Related Budget - Year 1**

54

- **Additional Personnel Budget Year 1**

57

**Research & Related Budget - Year 2**

58

- **Additional Personnel Budget Year 2**

61

**Research & Related Budget - Year 3**

62

- **Additional Personnel Budget Year 3**

65

**Research & Related Budget - Year 4**

66

- **Additional Personnel Budget Year 4**

69

**Research & Related Budget - Year 5**

70

- **Budget Justification**

73

**Research & Related Budget - Cumulative Budget**

78

**Research & Related Budget - Consortium Budget (Subaward 1)**

79

**PHS 398 Specific Cover Page Supplement**

96

**PHS 398 Specific Research Plan**

98

- **Introduction**

99

- **Specific Aims**

100

- **Research Strategy**

101

**Human Subjects Sections**

113

- **Protection of Human Subjects**

113

- **Women &Minorities**

117

- **Planned Enrollment Table**

118

- **Children**

119

**Multiple PI Leadership Plan**

120

**Bibliography & References Cited**

121

**Consortium/Contractual**

126

**Letters of Support**

127

**PHS 398 Checklist**

139
RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved?  
   ☒ Yes  ☐ No
   1.a. If YES to Human Subjects
   Is the Project Exempt from Federal regulations?  ☐ Yes  ☒ No
   If yes, check appropriate exemption number.  1  2  3  4  5  6
   If no, is the IRB review Pending?  ☒ Yes  ☐ No
   IRB Approval Date: ________________________________
   Human Subject Assurance Number: ________________________________

2. * Are Vertebrate Animals Used?  ☐ Yes  ☒ No
   2.a. If YES to Vertebrate Animals
   Is the IACUC review Pending?  ☐ Yes  ☒ No
   IACUC Approval Date: ________________________________
   Animal Welfare Assurance Number: ________________________________

3. * Is proprietary/privileged information included in the application?  ☐ Yes  ☒ No
   4.a. * Does this project have an actual or potential impact on the environment?  ☐ Yes  ☒ No
   4.b. If yes, please explain:
   4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?  ☐ Yes  ☒ No
   4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place?  ☐ Yes  ☒ No
   5.a. If yes, please explain:
   6. * Does this project involve activities outside of the United States or partnerships with international collaborators?  ☐ Yes  ☒ No
   6.a. If yes, identify countries:
   6.b. Optional Explanation:

7. * Project Summary/Abstract  1246-Project_summary.pdf  Add Attachment, Delete Attachment, View Attachment
   8. * Project Narrative  1247-Relevance.pdf  Add Attachment, Delete Attachment, View Attachment
   9. Bibliography & References Cited  1248-References.pdf  Add Attachment, Delete Attachment, View Attachment
   10. Facilities & Other Resources  1249-Facilities.pdf  Add Attachment, Delete Attachment, View Attachment
   11. Equipment
   12. Other Attachments  Add Attachments, Delete Attachments, View Attachments

Other information

Page 6
Project Summary

Surrogate decision-making by family caregivers is highly stressful and emotionally burdensome, in part because caregivers often feel unprepared to make surrogate decisions. It is not known which advance care planning (ACP) process best prepares caregivers for this role. The main purpose of this study is to evaluate whether family caregivers of patients with life-threatening illnesses are better prepared and have better experiences with surrogate decision-making: 1) when they engage in a structured ACP process together with patients (versus when patients engage in ACP alone); and 2) when they use an online decision aid for ACP (versus using standard ACP). In doing so, we will also examine: 3) interactions between these factors.

Using a 2 x 2 factorial design, 200 patient/family-caregiver dyads will be enrolled in a randomized, controlled trial, and assigned to 1 of 4 groups: Group 1: Standard ACP Alone, where the patient (but not family caregiver) uses standard ACP materials to engage in ACP; Group 2: Decision Aid Alone, where the patient (but not family caregiver) uses the decision aid to engage in ACP; Group 3: Standard ACP Together, where the patient and family caregiver use standard ACP materials together; and Group 4: Decision Aid Together, where the patient and family caregiver use the decision aid together.

There will be 3 study visits: Visit 1, where patients (+/- family caregivers) engage in ACP using either standard materials or the decision aid; Visit 2, where patients and family caregivers independently complete hypothetical vignettes and then caregivers are interviewed; and Visit 3, where family caregivers (but not patients) are interviewed about their experience with, and sense of preparation for, surrogate decision-making.

We hypothesize that engaging in ACP Together (patient + family caregiver) will be superior to patients engaging in ACP Alone, and that using the online Decision Aid will be superior to using Standard ACP. We further anticipate that engaging in ACP Together using the Decision Aid (Group 4) will be superior to the other 3 groups with regard to family caregiver: 1) self-efficacy; 2) knowledge; 3) depth of communication about ACP; 4) agreement between their decisions on the vignettes and patients' decisions; 5) understanding of how surrogate decisions should be made; and 6) satisfaction with the ACP process. We also expect that compared to Groups 1-3, family caregivers in Group 4 will report: 7) less distress; 8) less decisional conflict; 9) greater satisfaction with decisions; and 10) better experiences with surrogate decision-making.

Achieving our study aims will determine whether family caregivers who use an online decision aid to engage in ACP Together with patients who have life-threatening illnesses are better prepared and have better experiences with surrogate decision-making. If the answer is yes, as we anticipate, this research has the potential to address a critical public health concern by establishing a readily accessible, reliable, and cost-effective mechanism for family caregivers and patients to engage in advance care planning that works.
Narrative:

If the aims of this project are achieved, we will have shown that an advance care planning intervention can decrease the considerable distress experienced by family caregivers who serve as surrogate decision-makers for their seriously-ill loved ones. Furthermore, we will have identified a practical, exportable strategy for helping millions of caregivers prepare for their roles as surrogate decision-makers.
Facilities
The facilities described below provide the central infrastructure for data collection, analysis, and administration for our proposed study.

PENN STATE COLLEGE OF MEDICINE / PENN STATE MILTON S. HERSHEY MEDICAL CENTER

The Penn State College of Medicine and the Penn State Milton S. Hershey Medical Center occupy different areas of the same building complex. They have separate administrative structures, however they function as a unified enterprise for teaching and research.

Academic Departments
The investigators for this proposed project have a long history of collaboration, along with seamless Information Technology resources across departments, clinical centers, and campuses. In addition, the two clinician PIs (Michael J. Green, MD MS and Benjamin H. Levi, MD PhD) share the clinical environment with the other clinical collaborators on a daily basis.

Department of Humanities at Penn State College of Medicine
Drs. Green and Levi occupy private offices 15 feet apart from each other in the Department of Humanities on the 1st floor of the Penn State College of Medicine/Penn State Milton S. Hershey Medical Center. The Humanities Department has approximately 3,000 square feet of office space, including work-stations for support staff, equipment, and private offices for faculty. Co-Investigator Penrod has a dual academic appointment in the College of Nursing at University Park and the Department of Humanities. The Study Coordinator and Project Assistant have office space within the Department of Humanities, with password-protected computer files and locked file cabinets for the study.

Department of Public Health Sciences at Penn State College of Medicine
Co-Investigators Farace and Mauger are faculty members of the Department of Public Health Sciences (DPHS), each occupying a private office in the Academic Support Building ~600 yards from the main building of the Penn State Milton S. Hershey Medical Center. Shuttle service is provided 12 hours per day every 15 minutes. DPHS occupies 17,400 square feet of space at Penn State's College of Medicine, including 1,200 square feet in the Penn State Hershey Cancer Institute building, which opened in June, 2009. This space is divided into a set of private offices, partitioned work areas, a conference room, printing and file storage room and a secretarial area. There are five high-speed copiers, four fax machines, four Polycom® SoundStation® speakerphones and four scanners.

Data storage and management will utilize the Web-based Universal Questionnaire (WEB-UQ) application that was created by the Department of Public Health Sciences to help researchers design web-based data collection instruments, and organize data collection. Access to the secure WebUQ web site is restricted based on unique usernames, passwords, and role assignments within an investigator's account. Data transmissions over the Internet are encrypted using a 128-bit Secure Sockets Layer (SSL) encryption standard for which DPHS has its own security certificate. The SSL protocol provides data security layered between application protocols such as Hypertext transfer Protocol (HTTP) and Transfer Control Protocol/Internet Protocol (TCP/IP). This security protocol provides data encryption, server authentication, message integrity, and client authentication for a TP/IP connection. Data are stored, backed-up, and maintained on a DPHS server in an ORACLE database management system.

Penn State Hershey Cancer Institute
Co-investigator Schubart is a faculty member at the Penn State Hershey Cancer Institute, with a secondary appointment in the Department of Public Health Sciences. The Penn State Hershey Cancer Institute is located in the main hospital building at the Milton S. Hershey Medical Center (See Clinical Sites below for further description of facility).

Computer
The PIs have individual Apple workstations and laptops equipped with Windows XP. Files are easily transferred between PIs and all collaborators through email and a research server dedicated to this project. Co-Investigators Farace and Penrod use standard desktop personal computers. Firewall protection is provided
by Penn State College of Medicine. Public Health Sciences, the home department for co-investigator Mauger and the data management resource for the study, uses an integrated network of Microsoft Windows XP and Sun Solaris computing platforms. The department employs a high-speed, high-capacity tape backup system utilizing Advanced Intelligent Tape (AIT) technology. Incremental backups are performed on a nightly basis, and full backups are run each weekend. Backup tapes are stored in a secure location off-site in accordance with best practices for disaster recovery. Access to the network is controlled by various measures, which at a minimum consist of username and password authentication. Information transmitted across nonsecure networks such as the public internet is secured via Secure Sockets Layer (SSL) or Virtual Private Network (VPN)/Internet Protocol Security (IPSec) encryption. A Cisco PIX firewall surrounds the network and protects it from internet-based intrusion attempts. The department employs anti-virus software at the e-mail gateway, server and desktop level in order to protect its systems from infection by computer virus.

Clinical Sites
The following clinical centers at the Penn State Milton S. Hershey Medical Center were essential for our highly successful recruitment of patients for our prior and ongoing studies on advance care planning. We are pleased that this collaboration will continue for the proposed study, and letters of support are attached to this application.

The Penn State Hershey Heart and Vascular Institute ranks as one of the top 100 cardiovascular hospitals in America and is the leading provider of cardiovascular care in central Pennsylvania. The Penn State Hershey Heart and Vascular Institute employs 30 Cardiologists, 4 Intensivists, 5 Cardiothoracic Surgeons, 2 Vascular and Endovascular Surgeons, 4 Vascular Radiologists, 4 Heart Anesthesiologists, and 2 Vascular Anesthesiologists. The I. O. Silver Cardiovascular Clinic is a 3500 sq. ft. facility directly connected to the Penn State Milton S. Hershey Medical Center and College of Medicine. Patients will be screened and recruited from a heart failure specialty clinic within the Heart and Vascular Institute at the Penn State Milton S. Hershey Medical Center. It serves as an outpatient site for cardiovascular specialists, where there are 4 cardiologists who specialize (full time) in heart failure. This group provides care to 1,000 individual patients, over 90% of whom have chronic heart failure, accounting for nearly 3,000 outpatient visits annually. The Heart Failure group has successfully participated in over 50 clinical research trials in the past 10 years, demonstrating their capability to successfully recruit patients for heart failure studies. In a brief feasibility study, we successfully recruited from this institute 7 patients with Class III or IV congestive heart failure to complete our online Decision Aid and pre-/post-instruments. We look forward to further success in recruiting from this facility, especially with the support of our co-investigator, Dr. John Boehmer (Director, Heart Failure Clinic), whose letter of support is included in this application.

The Penn State Hershey Cancer Institute is a state of the art, 178,000 square foot facility that enhances key programs by consolidating clinical, research, and administrative services in a striking new architectural addition to the campus. On the first and second floors, the Penn State Hershey Cancer Institute offers a new radiation oncology suite, pharmacy, two outpatient clinics and infusion therapy areas. The Penn State Hershey Cancer Institute also has a clinical trials office, a clinical lab area that includes 4 phlebotomy stations, and an open lab area.

The recruitment of participants for our first study was successful because of our ongoing relationship with clinicians in the Penn State Hershey Cancer Institute. With the addition to our study team of Dr. Jane Schubart, an investigator with an academic appointment in the Cancer Institute, we expect to further enhance our previous recruitment strategy. Within the Penn State Hershey Cancer Institute, Dr. Schubart has access to services provided by the Community Sciences and Health Outcomes (CSHO) Core. The CSHO Core provides descriptive data on behavioral risk factors, tumor incidence, patient treatment patterns, and outcomes of cancer care in the Penn State Hershey Cancer Institute catchment area; assists in the design and conduct of community-based research, including accessing underserved and minority populations in the Penn State Hershey Cancer Institute catchment area; assists in the selection, use and interpretation of participant-reported outcome measures such as health-related quality of life measures across the spectrum of cancer research; and assists with systematic dissemination of research findings and evidence-based strategies to constituent communities. CSHO Core faculty collaborate with the Penn State Hershey Cancer Institute investigators to develop research proposals for extramural funding related to cancer prevention, etiology, treatment, and outcomes. For this project, the involvement of Dr. Schubart will be invaluable, not only for her contribution to
study design and procedures, but also for her involvement in the Penn State Hershey Cancer Institute, and her relationships with physicians from clinics important to the recruitment success of this project.

**The Penn State Hershey Pulmonary, Allergy, and Critical Care Medicine Department** combines pulmonary and critical care medicine and offers care for acute and chronic pulmonary disorders. Outpatients are seen in the University Physician Center (UPC), Suite 2400. This facility has 13 exam rooms, 8 attending physicians, and 9 fellows. Additionally, the clinic employs 4 RN/LPS, front desk staff and a full-time administrative director. The UPC pulmonary service has full pulmonary function support, including a pulmonary function lab to evaluate patients with chronic obstructive pulmonary disease (COPD) and other lung diseases. Approximately 770 patients/year with Stage III or IV COPD are seen at this site, and in a brief feasibility study, we successfully recruited 22 such patients to complete our online Decision Aid and pre-/post-instruments. With co-investigator Dr. Rebecca Bascom (Professor, Division of Pulmonology) collaborating on this project, we expect that we will be even better poised to enroll participants from Pulmonary Medicine at the Milton S. Hershey Medical Center.

The **General Clinical Research Center (GCRC) of the Pennsylvania State University** has been supported by a grant (M01-RR10732) from the National Center for Research Resources of the National Institutes of Health to provide personnel and facilities for investigator initiated peer-reviewed research with human subjects. The objectives of the GCRC are to facilitate the transfer of basic knowledge generated in research laboratories to the clinical arena, to elucidate pathogenic mechanisms of disease, and to evaluate new modes of patient management.

The GCRC resides in the main hospital of the Penn State Milton S. Hershey Medical Center. It is convenient to the Penn State College of Medicine offices, as well as clinical centers where recruitment will take place. It encompasses 6800 square feet and includes 5 patient exam rooms, an interview/consult room, a DXA room, 2 procedure rooms, 3 infusion sleep rooms and an exercise room. The GCRC provides outpatient rooms, expert support personnel including nurses, medical assistants, research techs, computer system manager, database management design and support, biostatistical support; and supplies and equipment necessary to perform quality clinical research studies. Since 1995, over 331 different protocols and 94 investigators have used the GCRC facilities at the Penn State Milton S. Hershey Medical Center. The GCRC hosts investigators funded by NIH and other federal, state and local agencies as well as by the private sector.

The GCRC was fundamental to the successful enrollment and administration of study procedures to participants in our "healthy adult" feasibility study, as well as in our ongoing American Cancer Society-funded study. Our Research Coordinator has forged a congenial and professional relationship with GCRC staff, and we expect that to continue and grow in the proposed study.

A skilled research nursing staff of 5 registered nurses is available Monday-Friday from 7:30 AM to 4:00 PM, with additional evening and weekend hours often available. The GCRC staff functions as a team working with other health care professionals to implement clinical research studies. The GCRC has an 800-number for recruitment and the GCRC nursing staff will assist scheduling appointments.

In addition, co-investigator David Mauger, PhD, has been the GCRC biostatistician for over 5 years. His guidance in study design and analysis and his experience in the GCRC is valuable to the study investigators because of his familiarity with GCRC procedures and capabilities.

**THE PARTNERS HEALTHCARE SYSTEM CENTER FOR CLINICAL & QUALITY ANALYSIS, BOSTON**

We will rely heavily on the facilities of our co-investigator, Lisa Lehmann, MD PhD, for recruitment of minorities to our study, given the relatively limited availability of minorities in Central Pennsylvania. The Partners Network is a nationally and internationally recognized center of excellence for evaluating the impact of information technology in clinical practice. It includes two large teaching hospitals, Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH), and several smaller community hospitals. In addition, it includes Partner's Community Health Care, a network of approximately 700 community-based physicians throughout the region. A substantial portion of patients seen at the BWH are non-Caucasian (>30%), and BWH has a
centralized clinical data registry (the Research Patient Data Registry) that allows (IRB-approved) querying by clinical and demographic variables. This electronic database will allow us to identify racial and ethnic minorities who meet eligibility criteria for our study. Letters of support from the relevant clinical enterprises at BWH are attached to this application.

Brigham and Women’s Hospital (BWH) and Massachusetts General Hospital (MGH) are the founding members of Partners HealthCare System, a not-for-profit integrated delivery system. BWH and MGH are major teaching affiliates of Harvard Medical School. Both are well-respected leaders in tertiary and quaternary care and have consistently been named among the country’s best hospitals by U.S. News and World Report. Over the last 10 years, BWH has been either the largest or second largest non-university recipient of research funding from the National Institutes of Health, and MGH conducts the largest hospital-based research program in the United States.

Furthermore, Dr. Lehman is a member of the Division of General Internal Medicine (DGM), at BWH. The DGM has the resources necessary to carry out numerous research projects and has extensive experience in performing multidisciplinary research, including clinical epidemiology, health services research, and analyses of large databases. DGM maintains photocopying machines, fax machines and administrative support. The Countway Library of Harvard Medical School (located across the street from BWH) will also be readily available to obtain relevant literature. The division also includes an experienced epidemiologist and biostatisticians, as well as programmers and research assistants, and has detailed information systems used for patient care and data storage across the network. Statistical software available in the division includes SAS (with Interactive Matrix Language and Graphics Modules), Stata, and Sudaan. The division is interconnected on an Ethernet network, and all Windows workstations are connected to this network.
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<td>4. Inclusion Enrollment Report</td>
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<td>5. Progress Report Publication List</td>
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<td>7. Inclusion of Women and Minorities</td>
<td>1255-Women_Minorities.pdf</td>
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<td>8. Targeted/Planned Enrollment Table</td>
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<td>10. Vertebrate Animals</td>
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<td>11. Select Agent Research</td>
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<td>15. Resource Sharing Plan(s)</td>
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<td>16. Appendix</td>
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List of Research Plan Attachments
Specific Aims: This application responds to FOA PA-09-122, Research on Clinical Decision Making in People with or at Risk for Life-Threatening Illness. In so doing, it addresses priorities outlined in the 2004 NIH State of the Science Conference Statement on Improving End-of-Life Care,\(^1\) as well as the 2008 report from the US Department of Health and Human Services on advance care planning.\(^2\) Both reports describe the task of preparing family caregivers for their role as proxy decision-makers as a critical public health concern.

**Our long-term goal** is to help family caregivers of seriously ill patients be better prepared to serve as surrogate decision-makers when their loved ones can no longer make medical decisions for themselves. Research shows that family caregivers find surrogate decision-making highly stressful and emotionally burdensome, in part because they feel unprepared for surrogate decision-making. To date, no studies have determined which advance care planning (ACP) process best prepares caregivers for this role. Our prior work shows that a computer-based decision aid can help patients make more informed decisions and communicate their wishes more effectively. We now propose to determine if family caregivers of patients with life-threatening illnesses are better prepared for surrogate decision-making: 1) when they engage in a structured ACP process *together* with patients; and 2) when they use this online decision aid for ACP. This will be accomplished via a randomized, controlled trial with a 2 x 2 factorial design comprising 4 groups:

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<tr>
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<th>Decision Aid</th>
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<tr>
<td>Patient Alone</td>
<td>Group 1</td>
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<td>Group 2</td>
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<td>P+C Together</td>
<td>Group 3</td>
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<tr>
<td>Group 4</td>
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The specific aims are:

**Aim 1:** To establish that family caregivers of patients with life-threatening illnesses are better prepared for surrogate end-of-life decision-making when they engage in advance care planning (ACP) *together* with patients (Groups 3 & 4), versus when patients engage in ACP Alone (Groups 1 & 2).

*Hypothesis 1:* Family caregivers will be better prepared to serve as surrogates when ACP occurs *together* (caregiver + patient) compared to when ACP occurs Alone (patient only) as measured by caregivers:

- i) Self-efficacy (re: making surrogate medical decisions for a loved one)
- ii) Knowledge (re: surrogate responsibilities and end-of-life medical conditions and treatments)
- iii) Reported depth of communication with patients (frequency, content, helpfulness of discussions)

*Hypothesis 2:* Family caregivers' accuracy of medical decisions made on behalf of patients will be superior when ACP occurs *together* (caregiver + patient) versus Alone (patient only), with accuracy measured by concordance between caregivers' and patients':

- i) Medical treatment decisions for hypothetical clinical vignettes (content of decisions)
- ii) Decision control preferences (process of decision-making)

*Hypothesis 3:* Family caregivers' stress associated with actual (i.e., real-life) surrogate decision-making will be decreased when ACP occurs *together* (versus Alone), as measured by caregivers:

- i) Distress (depression, anxiety, caregiver strain, impact of events)
- ii) Decisional conflict
- iii) Satisfaction with decision
- iv) Reported experience with surrogate decision-making

**Aim 2:** To establish that an online Decision Aid for ACP (Groups 2 & 4) is superior to Standard ACP (Groups 1 & 3) at preparing family caregivers for surrogate decision-making.

*Hypothesis 4:* Family caregivers will be better prepared (H1, H2) and will experience less stress (H3) after using an online Decision Aid compared to Standard ACP, as measured by each of the Aim 1 outcomes.

*Hypothesis 5:* Family caregivers' satisfaction with the ACP process will be superior for those who use an online Decision Aid compared to those who use Standard ACP, as measured by caregivers:

- i) Satisfaction with advance care planning (ACP)
- ii) Evaluation of the online advance care planning tools

**Aim 3:** To establish that family caregivers are better prepared for surrogate decision-making when they engage in ACP using an online Decision Aid/Together with patients (Group 4) compared to those who use Standard ACP (Groups 1 & 3) or patients who use the online Decision Aid/Alone (Group 2).

*Hypothesis 6:* There will be a significant, positive interaction between ACP Together and use of the Decision Aid, as measured by superior Group 4 outcomes (as per the above measures) compared to Groups 1-3.
A. Significance

A1. Why This Problem is Important. Each year ~2.5 million people die in America and as many as 70% of these individuals lack decision-making capacity when end-of-life medical decisions need to be made. In most cases, family members serve as surrogate decision-makers when loved ones cannot make their own medical decisions. But family caregivers often feel ill-prepared for making surrogate decisions, with many describing these life and death decisions as extraordinarily stressful and emotionally burdensome. Anxiety and depression are higher among caregivers than among patients themselves, with stress levels exceeding those of survivors of ferry disasters, home fires, and major constructions accidents. In one study of caregivers who made surrogate end-of-life treatment decisions, 82% suffered post-traumatic stress disorder symptoms, and a recent meta-analysis demonstrates that the burden associated with surrogate decision-making is widespread and often long-lasting. Many sources of caregiver stress during end-of-life care have been identified, including time and logistics, physical tasks, financial costs, uncertainty about prognosis, guilt associated with decision-making, and lack of knowledge about what the patient would have wanted. This proposal addresses one significant yet understudied source of stress: feeling unprepared to serve as a surrogate decision-maker.

A2. Limitations of Standard Advance Care Planning (ACP). Historically, efforts to improve the process of surrogate decision-making have focused on patients creating advance directive documents that accurately represent their wishes. The intention of this is to help family caregivers who make surrogate decisions (and tend to inaccurately predict patients’ wishes) make important treatment decisions that are more consistent with patients’ goals and values, and thereby help avoid ill-advised decisions and/or unwanted and costly medical care. But despite recent evidence that advance directive documents can increase the likelihood that patients will actually receive the medical care they wanted, traditional approaches to advance care planning (ACP) have fallen short on multiple counts. Less than a third of people actually document their wishes, so advance directives often do not accurately reflect patients’ values and preferences, and perhaps most importantly, standard approaches to ACP do not sufficiently engage individuals in the kinds of discussions needed to effectively prepare patients, family caregivers, and others for end-of-life decisions.

Standard approaches to ACP typically involve the use of a living will form with or without additional printed materials that describe common end-of-life medical conditions and interventions, legal and medical terms, and sometimes pose thought-provoking questions. What is not well established is which approach to ACP can best improve the process of surrogate decision-making, or affect the burdens associated with it. The proposed project intends to address this issue by examining: 1) whether ACP processes that involve family caregivers and patients together can reduce the strain of surrogate decision-making, by helping caregivers be better prepared for making such decisions, and 2) whether an innovative, systematic approach to ACP using an online decision aid is more effective at doing so than standard approaches. (Throughout this proposal, “ACP” will refer to the process individuals engage in to reflect on and document their wishes for medical care.)

A3. How This Project Will Improve Knowledge and Practice. Studies have shown that the stress and burden associated with surrogate decision-making are decreased when caregivers have prior experience with surrogate decision-making and have a better understanding of patients’ wishes. One promising approach to preparing family caregivers for surrogate decision-making is to have well-trained, compassionate professionals lead discussions with patient/family dyads (R01 NR010733/Nolan). However, its exportability to communities nationwide is limited by the availability of trained personnel as well as the cost of in-person, professional-led ACP. To overcome these barriers, our study will use an innovative online decision aid for ACP that is designed to be readily accessible to anyone with internet access, emphasizes the process of decision-making, and encourages individuals to systematically explore their goals and values as they articulate their wishes for future medical care (see C4.7 for a description of our decision aid). We recognize that technological solutions are imperfect and cannot replicate the kind of compassionate and personal interaction that occurs between people. Nevertheless, a practical solution is needed for providing effective ACP in the absence of trained professionals, and we have designed a process that attempts to meet this need. The present study proposes to examine whether ACP using our Decision Aid is more effective when patients and caregivers engage in this process together compared to when patients do so alone or when a Standard approach to ACP is used.

B. Innovation

B1. How This Proposal Shifts Current Research and Practice Paradigms. Few studies have examined ways to reduce the burden of caregiver decision-making by helping better prepare family caregivers to make decisions on behalf of patients. To feel and be more prepared, family caregivers need to know more about what their loved ones would want when faced with a medical crisis, and more about their own role as surrogate decision-makers. The proposed study will address several gaps in current knowledge by introducing two
innovations that will be compared to a standard approach to ACP: 1) having caregivers and patients engage in ACP Together, and 2) using an online Decision Aid that provides a structured interaction involving education, values-clarification, and medical decision-making.

Because the number of individuals caring for family members with life-threatening illnesses will continue to grow as our society ages, it is increasingly important to identify best practices for reducing family caregiver stress associated with medical decision-making. This study represents an innovative joining of advance care planning, multi-media education, and online decision aids to improve caregiver self-efficacy (see C.3) for their role as surrogate decision-makers. If we can demonstrate improved outcomes when family caregivers and patients engage in ACP Together using an online Decision Aid, our intervention will have the potential to help millions of patient/caregiver dyads who must make life and death medical decisions under stressful conditions.

B2. Novelty of Our Approach and Intervention. The most successful initiatives for ACP involve in-person facilitated encounters, and require broad community buy-in, trained personnel, and significant investment and coordination. Because many communities lack the infrastructure and/or resources required for such initiatives, a more widely available strategy for ACP is needed. Our approach is innovative because it uses a free-standing, easily disseminated online intervention that provides individuals with a structured process for ACP without the need for trained facilitators or a community-based infrastructure. Our study also provides a rare opportunity to extend findings of two funded NINR studies (1 R21 NR008539/Green and 1 R01 NR016733-01A1/Nolan) to improve patient/family involvement in surrogate decision-making.

Unlike standard approaches to ACP, our online tool accommodates special needs (hearing, vision, etc.), can be accessed repeatedly in a self-paced and private manner, and provides interactive feedback to promote learning. This decision aid uses audio and video clips throughout; text written at a reading level of ≤6th grade; and values clarification exercises that ask users to imagine living with various physical and mental debilities in an effort to help them elucidate what matters to them and why. Additionally, our decision aid is the first ACP program to help translate individuals' values and goals into a medical decision by systematically weighing competing objectives via formal decision analysis, grounded in Multi-Attribute Utility Theory (MAUT). MAUT's premises are 1) when choosing between alternatives, the best choice maximizes positive outcomes and minimizes negative ones, and 2) a person's priorities can be accurately ranked using a mathematical formula that calculates his/her preferences for different aspects (or attributes) of choices. MAUT is particularly well-suited for ACP because of its ability to clarify individual attributes of a decision, weigh the relative importance of each attribute, and synthesize a person's diverse values and desires into a single choice that optimizes their preferences. Additional background about MAUT can be found in Appendix 1.

C. Approach

C1. Experience of Investigators. Successful implementation of the project aims requires a research team with expertise in many areas: conducting intervention studies on advance care planning; developing computer-based educational programs; recruiting seriously ill patients and family caregivers; and collecting and analyzing both quantitative and qualitative data. Toward this goal, we assembled an experienced team of highly collaborative investigators with the requisite background. PIs Michael Green, MD, MS and Benjamin Levi, MD, PhD are physician-researchers who have collaborated for >20 years and are experts in advance care planning, end-of-life decision making, and bioethics. Collectively, the research team has expertise in medicine (BL, LL, MG), nursing (JP, MN), bioethics (BL, LL, MG), health outcomes research (JS, EF), psychology (EF), and biostatistics (DM, EF). We have a productive collaborative track record researching surrogate decision-making, and other educational interventions, and family caregiving for patients with serious illnesses. Further details about the investigators' qualifications are found in the biosketch and budget justification sections. Throughout this proposal, "we" will refer to work done by PIs Green/Levi -- with or without additional colleagues. The following summarizes relevant preliminary studies.

C2. Preliminary Studies

C2.1. Experience Designing a Decision Aid for Advance Care Planning. For >15 years, we (BL & MG) have created education programs on advance care planning (ACP), including a state-wide ACP curriculum disseminated by the Geriatric Education Center of Pennsylvania; the Advance Directive Project, which has provided outreach education to >3000 people in Central Pennsylvania since 1999; and a multi-dimensional curriculum for teaching medical students about ACP. Such experiences led to the development of our decision aid for advance care planning (Making Your Wishes Known: Planning Your Medical Future), funded by NINR (R21 NR008798), and tested over a 7-year period. To create the program, we followed a systematic
approach, beginning with a literature review, focus groups, and script development, then incorporating a decision analysis algorithm, and alpha and beta testing with target populations. Detailed descriptions of the program and its development have been published (see Appendix 2 and C4.8). We encourage reviewers to access the program at www.makingyourwishesknown.com (log on as a test user).

C2.2. Experience Evaluating User Satisfaction With Diverse Populations. We have tested the ACP decision aid among diverse populations (healthy volunteers, n=49; patients with chronic diseases, n=36; and patients with amyotrophic lateral sclerosis, n=27). Users were highly satisfied (1=Very Dissatisfied, 5=Very Satisfactory) with how the decision aid: increased knowledge about ACP (mean=4.4), provided information about medical conditions and treatments (mean=4.2), clarified values and wishes (mean=4.2), helped them make important end-of-life decisions (mean=4.3), helped put their wishes into words (mean=4.4), and helped prepare them to discuss wishes with family (mean=4.3) and physicians (mean=4.1).

C2.3. Experience Using Vignettes to Measure Concordance. We used hypothetical vignettes to assess concordance between patients' wishes and others' surrogate decisions for them. In a pilot study of 19 healthy volunteers, the advance directive generated by our decision aid was shared with 3 randomly chosen physicians who then (with no other patient information) made treatment decisions for each of 6 hypothetical end-of-life clinical scenarios (total decisions per patient=32). The "consensus physician response" for each treatment decision was subsequently shared with the patient for his or her agreement and overall assessment of the surrogate decision-making. Patients agreed with the consensus physician response 84% of the time, including whether to provide mechanical ventilation (82% agreement) or CPR (82%). Across the scenarios, patients' overall rating of how well physicians translated their advance directive into medical decisions was 8.6 (1=Extremely poorly, and 10=Extremely well). This pilot demonstrated: 1) the feasibility of using vignettes to measure concordance, and 2) that the decision aid can promote agreement between patients and others (in this case physicians) regarding treatment decisions.

C2.4. Experience Using the Decision Aid to Improve Knowledge of Patients' Wishes. In an ongoing study among patients with amyotrophic lateral sclerosis (ALS), we are evaluating whether our decision aid: 1) improves patient knowledge and decision-making, and 2) increases the multi-disciplinary ALS team's awareness of patients' healthcare wishes. At baseline and again 3 months after using the decision aid, members of the ALS team discuss 3 hypothetical vignettes and come to consensus about patients' wishes for end-of-life medical care. Preliminary data from 27 patients show: 1) increased post-intervention agreement regarding 18 vignette-based decisions (55.6% → 92.6% concordance, p < .001) between the ALS teams' understanding of patients' wishes for treatment and patients' documented wishes, and 2) significant pre-post improvement in patient knowledge about ACP (49.6% → 65.6% correct responses; p < .001). This demonstrates the feasibility of using the decision aid among patients with life-threatening illness and its usefulness for increasing others' knowledge of patient wishes.

C2.5. Experience Recruiting Minorities, Patients with CHF, COPD, and Advanced Cancer. We have tested our recruitment strategy by conducting pilot studies among patients with severe congestive heart failure (CHF n=7) and chronic obstructive pulmonary disease (COPD n=22), as well as inner-city African-Americans (AA's n=18). We encountered no difficulties recruiting participants or having them complete the online ACP decision aid. Participants were highly satisfied with the overall experience (9.6 for CHF/COPD, 8.9 for AA's; 1=not at all satisfied, 10=extremely satisfied), judged the advance directive generated by the decision aid to be highly accurate in articulating their values and wishes (9.5 for CHF/COPD, 8.8 for AA's; 1=not at all accurate, 10=very accurate); and use of the program did not adversely affect participants' anxiety or sense of hope (submitted). In an ongoing, 4-year (1/08–12/11) randomized controlled study (American Cancer Society, RSGHP-08-005-01-CPHPS/Green), we are evaluating whether use of our decision aid increases the likelihood that patients with advanced cancer receive end-of-life medical care consistent with their wishes. This study involves a 3-hour study visit and follow-up phone interviews, and uses a recruitment strategy similar to that proposed here. To date, 32 physicians have referred 1526 patients with advanced cancer (<2-year life-expectancy), of whom we have enrolled and retained 143 patients with cancer diagnoses including Lung (17%), Breast (13%), Brain (13%), Leukemia (11%), Liver (10%), Pancreatic (9%), Prostate (8%), and Colon/Rectal (7%). Despite the challenges of enrolling seriously ill patients into a study, we have established strong collaborative relationships with referring physicians and a very successful recruitment strategy that is on schedule for reaching our goal of 200 participants. This shows the feasibility of the patient component of our proposed recruitment. Of note, in contrast with the ACS study's focus on patients, the current proposal will primarily examine the impact of an ACP intervention on family caregivers. Additionally, the proposed study will begin after enrollment in the ACS study has completed, and as such, there will be no overlap in aims nor competition for recruiting study participants.
C2.6. Experience Conducting Research on Family Caregivers. Co-I Penrod has successfully conducted multiple qualitative studies\textsuperscript{75,76} on end-of-life care with caregiver/patient dyads, including examining ways to lessen caregiver distress and uncertainty dealing with healthcare providers (1R01NR010127-01A1/Penrod), and studying palliative care needs of spousal caregivers (1R15NR009976-01/Hupcey). In each of these studies family caregiver enrollment targets were met without difficulty. In her current R01, >88% of family caregivers of patients with ALS, heart failure, and lung cancer agreed to participate, resulting in 52 participants in <6 months. Co-Is Schubart and Farace have conducted several studies of patients and family caregivers to examine caregiver burden (using in-depth, semi-structured interviews\textsuperscript{78,79} and strategies for reducing that burden (ACS IRG Award/Schubart, P30CA4479-11/Shaffrey & Farace). As a consultant, Nolan brings extensive experience studying patient/family caregivers dyads, including research on preferred styles of involvement in end-of-life decision-making of patients with advanced cancer, heart failure, and ALS (1R01NR010733/Nolan, 1R01NR5224/Nolan). Co-I Lehmann has experience with quantitative and qualitative research on patients with advanced cancer, focusing on communication surrounding prognosis and end-of-life care.\textsuperscript{80}

C2.7. Summary. Given the aging of the U.S. population and the tremendous strain experienced by family caregivers of patients with life-threatening illnesses,\textsuperscript{81-84} it is increasingly important to find new ways to improve caregivers’ decision-making experience. We have assembled an eminently qualified team with the requisite expertise, experience, and track record to: 1) successfully recruit seriously ill patient/caregiver dyads to complete an ACP intervention, and 2) examine whether the burdens of surrogate decision-making experienced by family caregivers can be reduced through effective ACP. Moreover, we aim to establish that an interactive, multi-media decision aid for ACP is feasible as an online resource for family caregivers.

C3. Conceptual Framework for Caregiver-Surrogate Self-Efficacy. Our study is based on a conceptual model of family caregivers’ self-efficacy for decision-making that builds on a caregiver stress model developed by Pearlin.\textsuperscript{85} Self-efficacy is a component of Social Learning Theory referring to individuals’ beliefs about their capabilities to control events that affect their lives.\textsuperscript{86} Self-efficacy theory describes how people’s beliefs in their coping capabilities affect their motivation as well as experience of stress and depression in threatening situations. Perceived self-efficacy to exercise control over stressors plays a central role in one’s willingness to attempt difficult activities. A low sense of self-efficacy produces depression, anxiety, and avoidant behavior. Pearlin describes caregiver stress as a process encompassing four domains: the background and context of stress; the stressors and strains; the mediators; and the outcomes or manifestations of caregiving stress. Each domain has multiple components, such as social and economic characteristics of the caregiver, prior experience, and the composition of family networks. Primary stressors stem directly from the demands of caregiving. This often leads to other, secondary, role strains. Studies of caregivers and stress show that people exposed to similar stressors are affected in dissimilar ways.\textsuperscript{86} The mediators are the variables that explain some of this outcome variability. In our study, the strategies of engaging in ACP Together and the use of an online Decision Aid for ACP are hypothesized to enhance caregiver self-efficacy. This occurs by: 1) increasing caregiver knowledge of surrogate responsibilities and options for end-of-life medical treatments/conditions, and 2) providing an opportunity to participate in ACP with their loved one. Other direct outcomes predicted by this model include improved accuracy of decisions made by family caregivers, decreased caregiver stress, and improved caregiver satisfaction with decisions.

C4. Overall Strategy, Methodology and Analyses. Building on this conceptual model, the overarching goal of the project is to improve the process and experience of surrogate decision-making by family caregivers. While reducing caregiver burden is our primary objective, we have not found a feasible measure that separates the specific burden of surrogate decision-making from the general burden of caring for a sick loved one. Since feeling unprepared to make surrogate decisions is a major contributor to caregiver stress,\textsuperscript{12,13,14,15,16,86,87} our primary outcome is caregiver self-efficacy – i.e., caregivers’ assessment of their how well prepared they feel to serve effectively as a surrogate decision-maker (for which we have a specific, validated measure\textsuperscript{86}). As such the primary aim is to determine if caregivers are better prepared for being surrogate decision-makers when they engage in ACP Together with patients, versus when patients engage in ACP Alone. Using a 2 x 2 factorial design, we will also compare the efficacy of an online Decision Aid for ACP versus a Standard Approach to ACP, and thereby determine whether caregivers who engage in ACP Together with patients using the Decision Aid (Group 4) are better prepared than others (Groups 1, 2, and 3). Secondary outcomes include caregiver: knowledge of patients’ wishes, real-world experience with actual surrogate decision-making, caregiver stress, and overall assessment of the usefulness of ACP tools. Of note, though both the Decision Aid and Standard ACP will generate an advance
C4.1. Summary of Study Design. This is a randomized, controlled trial of an ACP intervention for family caregivers of patients with severe life-threatening disease. Using a $2 \times 2$ factorial design, we will test two equally important, and possibly related, propositions: 1) that participating in advance care planning Together (patient + caregiver) is superior to doing so Alone, and 2) that using an online Decision Aid is superior to Standard ACP. In doing so, we will also examine interactions between these factors. As shown in Figure 1, patient/caregiver dyads will be assigned to one of four groups: Group 1: Standard ACP/Alone, where the patient (but not caregiver) engages in ACP (using Standard ACP materials); Group 2: Decision Aid/Alone, where the patient uses the Decision Aid to engage in ACP; Group 3: Standard ACP/Together, where the patient and caregiver engage in ACP Together (using Standard ACP materials); and Group 4: Decision Aid/Together, where the patient and caregiver use the Decision Aid Together. At Study Visit 1, patients with or without caregivers will engage in ACP using either Standard materials or the Decision Aid. Four weeks later at Study Visit 2, patients and caregivers will independently complete hypothetical vignettes, and investigators will conduct in-person interviews with caregivers. Subsequently, caregivers will be interviewed by phone every 8-12 weeks until they report having engaged in surrogate decision-making on behalf of the patient, after which caregivers (but not patients) will be asked to return for an in-person interview that will constitute Study Visit 3.

In this study, we define “engaging in decision-making on behalf of the patient” as any event for which family caregivers report being relied upon to make an important medical decision on behalf of the patient. We know from research that 44-89% of patients with terminal illnesses prefer to share decision-making with a family member when important decisions need to be made. Therefore, we will not require that the patient formally lack decision-making capacity in order for surrogate medical decision making to occur. To account for variability of what constitutes “being relied upon” and what counts as an “important medical decision,” we will qualitatively explore these concepts during Study Visit 3.

**Figure 1: Schematic for Preparing Family Caregivers for End-of-Life Decision-Making Study**

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Referrals (from oncologists, cardiologists, and pulmonologists)

Informed consent and screening

Pre-intervention measures

Screen fail (no longer eligible)

Study Visit 1
(2-3 hours)

Group 1: Standard ACP Alone (n=50)
Group 2: Decision Aid Alone (n=50)
Group 3: Standard ACP Together (n=50)
Group 4: Decision Aid Together (n=50)

Patients complete post-intervention measures

Patients and Caregivers complete post-intervention measures

Study Visit 2
(60-90 Minutes)

Patients and Caregivers (separately) complete vignettes, then
Caregivers complete self-efficacy measures, then
Caregivers are interviewed re: depth of communication

Caregivers participate in telephone interviews
Every 8-12 weeks until they have engaged in decision making on behalf of the patient

Caregivers participate in interview after surrogate decision making

Study Visit 3
(1 hour)
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Research Strategy
C4.2 Study Population. To have 200 complete patient/caregiver dyads at the study's end, we will screen 2000 dyads (and enroll 333 of them) from the Penn State Hershey Medical Center (PSHMC) and Brigham and Women's Hospital (BWH).

**Patient Inclusion Criteria:**

1. ≥18 years of age
2. Diagnosis of advanced cancer (Stage IV disease or having an estimated survival of <2 years) or severe congestive heart failure (Class III or Class IV as per New York Heart Assoc.) or severe lung disease (Stage III or Stage IV COPD by modified GOLD Spirometric Classification).
3. Able to read and understand English at an 8th grade level (word 26 on reading subtest of validated Wide-Range Achievement Test-3 (WRAT-3)).
4. Neuro-cognitively able to engage in ACP (score >23 on Folstein Mini Mental State Exam (MMSE)).
5. Not more than moderately depressed (score of <20/63 on Beck Depression Inventory-II (BDI-II)).

Patients with moderate/severe congestive heart failure, chronic lung disease, or advanced cancer were chosen as the study population because they have in common a high risk for life-threatening medical complications that are likely to precipitate surrogate decision-making on their behalf (i.e., a >50% chance of dying or losing decision-making capacity within a 24-month period). Based on our prior work, computer inexperience will not hinder enrollment, and we anticipate that <5% of eligible participants will screen-fail due to cognitive impairment, significant depression, or low literacy.

**Caregiver Inclusion Criteria:**

1. ≥18 years of age
2. Identified by the patient as the family caregiver who will be the patient's primary surrogate decision-maker (if non-cohabitant, must have in-person interaction with patient at least once weekly)
3. Able to read and understand English at an 8th grade level (word 26 on reading subtest of validated Wide-Range Achievement Test-3 (WRAT-3)).
4. Neuro-cognitively able to engage in ACP (score >23 on Folstein Mini Mental State Exam (MMSE)).

For this grant, family caregivers are defined as family members or close personal friends who have at least weekly in-person interaction with the patient—with most named caregivers expected to be adult children (49%) or spouses (33%). A single decision-maker is identified for data collection purposes only; to accommodate patients who may be uncomfortable assigning surrogate decision-making authority to just one individual, we will explain that the named caregiver may obtain feedback from others.

C4.3. Study Sites. The primary study site, Penn State Milton S. Hershey Medical Center (PSHMC), is a referral and primary care center for a large portion of Pennsylvania, and the clinical enterprise for the Penn State College of Medicine. The secondary study site, Brigham and Women's Hospital (BWH), is a teaching affiliate of Harvard Medical School located in Boston. Details about both sites are found in the "Facilities" section.

C4.4. Recruitment – Step 1: Patients. Using recruitment methods that have been successful in our current ACS study, we will prospectively review referring physicians' clinic schedules and patients' diagnoses to identify eligible patients, and will send a letter of introduction (see Appendix 3) on behalf of the referring physician. The introduction will include a stamped, return "opt out" letter that patients can mail to the PIs if they wish not to be contacted by researchers. If no opt out letter is returned within 3 weeks, the research assistant will telephone the patient to determine their interest in participation and to identify a family caregiver whom they wish to serve as their surrogate for medical decision-making in this study. Should the patient wish to identify more than one family caregiver, the research coordinator will explain that for data-collection purposes a single individual is necessary, but the named caregiver may seek feedback from others. Step 2: Caregivers. Following the phone call, patients will be sent an information packet to share with the family caregiver describing the study requirements and eligibility. Two weeks later, patients will be contacted, and interested patient/caregiver dyads will be scheduled for Study Visit 1. We will record basic demographic information on decliners to identify meaningful differences from participants.

During Study Visit 1, we will screen for eligibility and elicit informed consent from patients and family caregivers (see C.6 Screening and Appendix 4). Based on Nolan's and Penrod's prior research experience with patient/caregiver dyads, we anticipate contacting ~2,000 patients to retain 200 intact dyads (400 total subjects) at the end of the study. This assumes enrolling approximately 1 out of every 6 dyads contacted (n=333), and a 40% drop-out rate (i.e., the loss of 133 dyads) between Study Visit 1 and Study Visit 3.
At participating PSHMC cardiology, pulmonary and cancer outpatient clinics, approximately 2440 unique patients are seen annually who meet entry criteria -- Class III/IV congestive heart failure (830/yr), Stage III/IV COPD (850/yr), or advanced cancer (760/yr). With an expected 10-15% enrollment, we will be able to recruit 7 patients per month during years 1-4, meeting the end-study goal of 150 patients for PSHMC. We have achieved this enrollment rate in our current ACS study of patients with advanced cancer, and our prior experience indicates that involvement in other studies will not hinder enrollment. We will provide a $50 payment to each research participant for each visit (i.e., $250 total per completed patient/caregiver dyad).

To remedy the fact that Central Pennsylvania has a relatively small ethnic and racial minority population, 50 patient/caregiver dyads (25% of total) will be African-American and/or Hispanic individuals recruited from BWH under the leadership of Co-I Dr. Lehmann. We will use a similar recruitment strategy at BWH, except that at BWH the first level of screening will be done via their Research Patient Data Registry (RPDR), a centralized clinical data registry that allows IRB-approved querying by clinical and demographic variables. At BWH there are ~1200 eligible patients/year in the target disease clinics, and >30% of the patient population is registered as racial or ethnic minorities. Given the ability to recruit subjects by race, ethnicity, and gender through the RPDR, we anticipate being able to enroll an average of 2-3 African-American or English-speaking Hispanic patients per month during years 1-4 to meet our end-study goal.

C4.5. Randomization. Dyads will be assigned randomly to 1 of 4 groups (see Figure 1). The randomization scheme will include 3 stratification factors—medical condition (CHF, lung disease, cancer), race/ethnicity, and site (Boston, Hershey)—to ensure balance across intervention groups with respect to the most important covariates. Group assignment will be made via a computerized randomization algorithm.

C4.6. Study Activities & Treatment Fidelity. Study visits will each take place at the General Clinical Research Center (GCRC) at either PSHMC or BWH. To ensure standardization, research staff (present during all study visits) will receive uniform training, will follow a script and checklists, and will be periodically monitored by one of the PIs. Potential problems will be handled as discussed in C8.5 and in the Data and Safety Monitoring Plan. For descriptions of measures see Table 1, for timing of measures see Section C5.1, and for draft of all measures see Appendix 4. Time estimates are based on our preliminary work.

Study Visit 1 (2-3 hour appointment)
1. Investigators obtain written informed consent from patients and caregivers
2. Patients and caregivers complete screening measures (13 minutes)
3. Patients and caregivers complete pre-intervention measures (28 minutes)
4. Participants complete ACP (1-2 hours; will record actual time spent)
   a. Groups 1 & 2: patients (Alone) engage in ACP (Standard ACP or Decision Aid)
   b. Groups 3 & 4: patients/caregivers engage in ACP Together (Standard ACP or Decision Aid)
5. Participants complete post-intervention instruments (15 minutes)
   a. Groups 1 & 2: patients (Alone) complete all post-intervention measures
   b. Groups 3 & 4: patients/caregivers independently complete post-intervention measures
6. Investigators provide copies of patient’s advance directive document to patient/caregiver dyads

Study Visit 2 (60-90 minute appointment --4 weeks after Study Visit 1, to allow patient/caregiver dyads time to digest information from Study Visit 1 and engage in discussions about ACP)
1. Patients and caregivers independently complete 6 hypothetical clinical vignettes and Decision Control Preferences scale (described below) (33 minutes) --Patient participation is complete
2. Caregivers (only) complete self-efficacy and knowledge measures (10 minutes)
3. Trained investigator (Schubart/Petrod or Lehmann) interviews caregiver to assess nature and extent of discussions regarding ACP since Study Visit 1 (~20 minutes) (see Depth of Communication, Appendix 5)

Follow-up Phone Interviews (8-12 weeks after Study Visit 2, and every 8-12 weeks thereafter)
1. Investigators interview caregivers by telephone using interview guide to ascertain whether caregivers have engaged in surrogate decision-making since last contact (see definition, C4.1), and assessment of caregiver anxiety and strain (15 minutes)
   a. If the caregiver has not engaged in medical decision-making on behalf of the patient, he or she will be asked a basic set of follow-up questions (see interview guide, Appendix 5) and will be called again in 8-12 weeks
   b. If the caregiver has engaged in medical decision-making on behalf of the patient since the time of last contact, he or she will be scheduled for Study Visit 3
Study Visit 3 (1 hour appointment -- final component of the study) (see interview guide, Appendix 5)

1. After caregivers have made surrogate decisions, investigators (Schubari/Penrod or Lehmann) will interview caregivers about decision-making experience

2. Caregivers complete various caregiver burden measures

C4.7. Description of Decision Aid. The online Decision Aid for advance care planning (ACP) is the PIs' program, Making Your Wishes Known: Planning Your Medical Future. It is an innovative approach to ACP that differs significantly from standard approaches. [36,86] Most obviously, it is an interactive multimedia program. More importantly, it emphasizes the process of ACP by providing an educational and reflective approach to pragmatic decision-making, rather than a checklist of decisions. It also includes values clarification exercises to help individuals reflect on their goals, values, and priorities; and it utilizes MAUT-based decision analysis to guide users through the process of making choices. By doing so, it translates their goals and values into a medical plan (in the form of an advance directive) that can be printed, distributed, and used for decision-making. Finally, it allows users to revisit and revise these decisions (if desired). Pilot studies show that users require ~106 minutes to complete the Decision Aid, and a detailed description can be found in Appendix 2. We encourage reviewers to access the program at www.makingyourwishesknown.com (log in as "test user").

C4.8. Description of Standard Advance Care Planning (ACP). The Standard ACP in this study consists of an educational pamphlet plus an online version of a standard living will form. This combination is similar to other studies' descriptions of "Standard ACP." [43,44,103] Far from being a straw man, this Standard ACP is likely superior to what patients typically encounter, since we will use ACP materials produced by the American Hospital Association (see Appendix 6) along with a modified version of Delaware's living will document [see https://webapp.bmc.ps.edu/ad/visitor/index.cfm] which we chose because Delaware is 1 of only 7 states to receive an "A" rating by Last Aesis for its advance directive materials. [103] Participants who want more information about ACP will be referred to hospital social services, as per standard practice at PSNMC and BWH.

C4.9. Description of Vignettes. The vignettes, which we have adapted from our prior studies (see Appendix 7), were written to represent end-of-life scenarios that patients with serious medical conditions commonly encounter—including severe infections, strokes, and accidents. Each vignette presents a hypothetical scenario that requires a decision to accept or decline potentially life-saving medical treatments. We chose to use these vignettes after a literature review and personal correspondence with Shalowitz (who reviewed hundreds of ACP vignettes [17]) revealed no standard end-of-life vignettes with sufficient clinical detail to simulate real-life scenarios or accurately measure patient preferences for end-of-life scenarios. Additionally, recent research suggests that compared to standard living will scenarios, detailed vignettes are more likely to identify individuals' true preferences. [33] Despite potential advantages of examining pre-post-intervention changes in treatment preferences, we will not administer the vignettes at Study Visit 1 (in addition to Visit 2) out of concern that the vignettes might serve as a confounder by influencing how participants subsequently engage in ACP.

C5. Data Collection, Analysis and Interpretation.

C5.1. Measures. Table 1 summarizes all measures used in the project, the time required to complete each, who will complete the measure, and when and how it will be administered (see Appendix 4 for details).

(i) Patient and Caregiver Demographics. This will include age, gender, education, religion, experience with computers, prior completion of an advance directive, and functional status. [103]

(ii) Caregiver Decision-Making Self-Efficacy Scale. Perceived self-efficacy is our primary outcome and involves people's beliefs in their capabilities to perform certain tasks. [66] Nolan et al. validated and modified a scale [88] based on Bandura's framework. [104] The scale indicates their confidence in 7 areas of decision-making: surrogacy, treatment, palliative care, spirituality, family, communication, and mortality. The total item score provides an overall measure of family caregiver decision-making self-efficacy. In Nolan's pilot test, the Cronbach's Alpha is .96 when the patient lacks decisional capacity.

(iii) Caregiver Self-Evaluation of Surrogate Decision-Making. This scale (modified to a retrospective assessment from Nolan's prospective instrument) measures caregivers' impressions of how well they performed as surrogates AFTER they have made decisions.

(iv) Knowledge. Validated 27-item multiple-choice knowledge test about advance care planning.

(v) Depth of Communication. This is a structured interview with caregivers to assess the frequency, content, and helpfulness of their discussions with the patient about advance care planning.

(vi) Concordance Score. This is a scorecard that compares patients' and caregivers' responses to 6 hypothetical clinical vignettes, resulting in a summative concordance score.

(vii) Decision Control Preferences (DCP) Scale. Validated set of captioned illustrations depicting one's desired level of involvement of family members, from no involvement to fully involved. [4,90,95,105,106]
Surrogate Decision-Making Activity. Structured phone interview administered by the research assistant to determine if the caregiver has engaged in surrogate decision-making since last contact.

Caregiver Depression. Validated Beck Depression Inventory-II (BDI-II).95

Caregiver Anxiety. Validated state anxiety subscale of the State Trait Anxiety Inventory (STAI).107

Caregiver Strain. Validated 15-item Zung Burden Interview (ZBI) short form.108

Stress/Trauma of Decision-Making. Validated 15-item Impact of Events Scale.11,109,110

Caregiver Decisional Conflict. The conflict that caregivers experience with regard to their surrogate decisions will be measured using the validated 16-item Decisional Conflict Scale.111

Caregiver Satisfaction with Decision. Overall satisfaction with surrogate decisions will be measured using the validated, 6-item Satisfaction with Decision Scale.112

Experience as Surrogate. This is a semi-structured caregiver interview assessing their experience with surrogate decision-making, including interactions with physicians.

Satisfaction with Advance Care Planning Process. This is a 12-item scale used in our prior research measuring satisfaction across 4 domains: 1) quality of information provided; 2) helpfulness in values clarification; 3) helpfulness in decision-making; and 4) helpfulness in communicating wishes.

Evaluation of Online Intervention will be measured with Ritterband’s validated instruments for assessing usability and impact of an online intervention.113-115

Table 1: Timing of Measures

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<td>v. Depth of communication</td>
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<td>P+C</td>
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<td>Phone interview</td>
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<td>x. Anxiety</td>
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<td>xi. Caregiver strain</td>
<td>ZBI short form</td>
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<td>Self+phone</td>
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<td>xii. Stress of decision-making</td>
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<td>xv. Experience as surrogate</td>
<td>Interview</td>
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<td>xvi. Satisfaction with ACP</td>
<td>Satisfaction w/ ACP</td>
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<td>xvii. Evaluation of online intervention</td>
<td>Evaluation and Utility tool</td>
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<td>P+C</td>
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P=Patient, C=Caregiver, D=Decliner

C5.2. Data Management. Quantitative data from both sites will be collected through self-administered questionnaires and vignette exercises, and will be cleaned, coded, and entered by the Research Assistant in Hershey into the Web-based Universal Questionnaire (WEB-UQ) application (see Facilities). Data management will be overseen by Dr. Mauger who is Division Chief of Biostatistics in the Department of Public Health Sciences at PSHMC, which created and maintains the WEB-UQ application.

C5.3. Quantitative Data Analysis. Analysis will be done using SAS version 9.2 (SAS Inc, Cary, NC). Initial data summarization will include descriptive statistics of patients'caregivers' baseline demographics, e.g., condition, gender, age, ethnicity, race, education, religion, marital status, place of residence, employment status, and
prior completion of an advance directive. Frequency distributions will be used to summarize categorical variables and mean, standard deviation, median, and interquartile range for continuous variables.

The primary outcome is caregiver self-efficacy, calculated as the mean score on the 7-item Caregiver Decision-Making Self-Efficacy Scale for Unconscious Patients. Pilot data from 21 individuals revealed a standard deviation of 14, consistent with previously reports. The primary analysis will examine the change in Self-Efficacy score from Study Visit 1 to Study Visit 2 (pre- vs. post-intervention) as the response variable. This study utilizes a 2x2 factorial design with ACP Together and Decision Aid as main effects, resulting in four treatment groups (Group 1=Standard ACP/Alone, Group 2=Decision Aid/Alone, Group 3=Standard ACP/Together, Group 4=Decision Aid/Together). Two-way analysis of variance (ANOVA) is the appropriate analysis method, testing for both main effects and interaction effects. One limitation of this design is that interaction effects can confound main-effect estimates. Therefore, before examining main effects, we will first test for interaction effect --using a 0.1 significance level because there is generally much less power for detecting interaction effect as compared to main effect. In addition, the purpose of the interaction test is to determine the form of the main-effects analysis and thus, represents a screening test rather than a standard hypothesis test. If the interaction effect is non-significant, the main effects will be tested in the two-way ANOVA framework (i.e., groups Group 1+2 vs. 3+4, and Groups 1+3 vs. 2+4). If the interaction effect is significant at the 0.1 level, then the main effects will be tested as if a 3-group design had been employed (Group 1=Standard ACP/Alone, Group 2=Decision Aid/Alone, Group 3=Standard ACP/Together) and pairwise comparison between each of the main effect groups and the control group will be made (i.e., Group 1 vs. 2 and Group 1 vs. 3); Group 4 does not factor into the analysis. The 2x2 design is much more powerful than the 3-group design if there is no interaction, but somewhat less powerful if there is an interaction. The primary analysis ANOVA model will include 4 covariates: patients’ prior completion of an advance directive and the 3 stratification factors used in the randomization procedure (medical condition, race/ethnicity and study site).

Secondary analyses will compare the intervention groups with respect to the other outcomes as summarized in Table 1. For measures collected pre-intervention and one time post-intervention, the change score will be the outcome. ANOVA will be used to compare groups for continuous outcomes and chi-square tests will be used to compare groups for binary or ordinal outcomes. Some of the outcomes, including the STAI and ZBI Instruments, will be collected at multiple times post-intervention. For these data, linear mixed-effects models will be used to characterize longitudinal differences between groups. Additional secondary analyses will examine the possible effects of demographic characteristics such as age, race or gender. For these analyses, analysis of covariance and logistic regression or ordinal logistic regression will be used instead of ANOVA and chi-square tests. These models can also be applied in the mixed-effects framework for the longitudinal data. Interaction terms between intervention group and covariates also can be introduced to explore possible effect modification --e.g., whether participants with certain characteristics display a greater intervention effect.

C5.4. Sample Size Considerations. The total sample size of 200 will yield at least 80% power to detect a treatment group difference in Self-Efficacy change of ≥5 points. This is based on the conservative assumption that interaction will be significant and that 3-group analysis will be required. If the interaction is not significant and two-way analysis is done, the power will be > 90%. These calculations are based on an intra-subject correlation of 0.7 between Visit 1 and Visit 2 Self-Efficacy scores. To the extent that there are systematic differences in the primary outcome between subgroups defined by the 3 stratification factors, and prior completion of an AD, the statistical power may be higher than anticipated because of the attendant reduction in the ANOVA residual error. However, in the absence of prior data on which to base power calculations adjusting for these factors, we have taken the conservative approach of assuming that there will be no systematic differences, meaning that sample size calculations are consistent with a "worst-case" scenario.

C5.5. Qualitative Data Analysis. Classic Grounded Theory methods will be used to examine caregiver stress during surrogate decision-making (Hypothesis 3) and whether they feel prepared to serve as surrogate (Hypothesis 1). This inductive process is appropriate to model phenomena about which little is known. Co-Is Schubart and Penrod, experienced qualitative researchers, will be responsible for this arm of the study. During Study Visit 3, qualitative interviews with all caregivers will be conducted by Schubari/Penrod in Hershey, and Lehmann in Boston. Interviews will be audio-recorded, transcribed verbatim, verified and cleaned of identifiers before entry into the dataset. Initial interviews will be critiqued for style and content to enhance the quality of the data. A team approach to analysis will be used, with meetings held at least bi-weekly via tele- or video-conferencing (ISJP/IL). Analytic techniques will include: open coding; assigning words or phrases that capture the meaning in the data (i.e., “memoing”); comparing open codes to create relevant categories; and selective coding around the core variable that will enable the development of coherent theoretical formulations that interpret the characteristics of caregivers’ stress and their assessment of how well-prepared they are to...
serve as surrogates. All team members will complete analyses independently, bringing insights to the team meeting. Using techniques of challenging members to support conjectures with data, the team will reach consensus regarding emergent categories/theoretical formulations. Since analysis and data collection occur simultaneously, emergent analytic insights will continually inform new data collection and the team will revert to theoretical sampling techniques in order to confirm, refute, or extend theoretical assertions. Data collection will continue until saturation of core categories. The software program ATLAS.ti will be used to facilitate data management. The product of this investigation will be an interpretive theory of caregivers’ perception of being prepared for and stress during surrogate decision-making.

C5.6. Triangulating Quantitative and Qualitative Data. The quantitative and qualitative nature of this study requires data analysis to be ongoing and iterative. A number of quantitative measures will allow our results to be compared to our prior work and to the work of Nolan and her colleagues, and qualitative data analysis will allow for the emergence of unexpected findings. The selection of the interview categories, however, were guided by the intent of the study and the theoretical constructs on which it is based. Therefore the final stage of analysis involves examining the qualitative findings for “fit” with the quantitative findings. For example, findings on the quantitative measures will be compared with responses to interview questions related to the various constructs (e.g., burden of surrogate decision-making, feeling prepared to make a decision). Divergent findings will be critically examined by the team and possible additional questions will be added to the qualitative interview guide. Interpretation of quantitative outcome measure scores will be “contextualized” by the narrative findings, with qualitative findings helping explain unexpected quantitative findings or adding support to expected findings.

C6. Study Timeline

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To achieve the aims, a 5 year time-frame is needed for two reasons: 1) to accommodate the complexity of recruiting, retaining, and coordinating dyads for up to 3 study visits— with up to a 40% drop-out rate between study visits 1 and 3; and 2) to provide the necessary time interval for interviewing family caregivers whose loved ones do not require surrogate decision-making right away.

C7. Expected Outcomes. We expect to find that engaging in ACP Together (patient + caregiver) will be superior to patients doing so Alone, and that using the online Decision Aid will be superior to using Standard ACP. Further, though we are not certain how these factors will interact, we anticipate that engaging in ACP Together using the Decision Aid (Group 4) will be superior to the other 3 groups with regard to caregiver: 1) self-efficacy; 2) knowledge; 3) depth of communication about ACP; 4) agreement (i.e., concordance) between their decisions on the hypothetical clinical vignettes and patients' decisions; 5) understanding of the patient's decision control preferences (i.e. how surrogate decisions should be made); and 6) satisfaction with the ACP process. We also expect that family caregivers in Group 4 will report: 7) less distress; 8) less decisional conflict; 9) greater satisfaction with decisions; and 10) better experience with surrogate decision-making.

C8. Potential Problems, Alternative Strategies, and Benchmarks for Success

C8.1. Recruitment of Patients and Caregivers. Recruiting severely ill patients and their family caregivers into this study can be challenging, given the sensitivity of the topic and the resistance of some individuals to talking about end-of-life decision-making. To address these concerns, we will implement a protocol we have rigorously piloted and successfully implemented in ongoing research with patients who have advanced cancer, heart failure, or COPD. This includes sending personalized letters from referring physicians to these patients, and expanding the referral network of 32 physicians with whom we already have strong working relationships. Data from our current AGS study (submitted), show that seriously ill patients value the opportunity to engage in ACP, doing so neither increases anxiety nor decreases helpfulness and physicians appreciate their patients’ involvement in our studies. Based on our experience, even a conservative estimate of enrolling 1 out of every 10 eligible patients will provide sufficient study participants to meet our goal.

C8.2. Recruitment of Minorities and Women. Though we have successfully recruited minorities in pilot studies, PSHMC’s small minority population (<5% of patients seen) poses a challenge to recruiting substantial numbers
of non-white participants at this site. For this reason, we have added a second study site in Boston, where they will exclusively recruit non-white participants. BWH has an electronic data base that allows researchers to query by diagnosis and race/ethnicity, and we will use this in our screening at that site. BWH will recruit a total of 50 minority participants into the study. We do not expect any challenges to recruiting women participants, since the target illnesses affect both genders, and an estimated 2/3-3/4 of family caregivers are female.\textsuperscript{118,119}

C8.3. Implementation Challenges and Proposed Solutions.

Discomfort with computers: While some older and chronically ill patients may be uncomfortable using computers, older adults are the fastest growing consumer segment of internet users,\textsuperscript{120,121} and accessing health-related information is common among patients with cancer,\textsuperscript{122} lung and heart disease,\textsuperscript{123,124} and their caregivers.\textsuperscript{125} Nevertheless, to address potential barriers to the use of an online intervention, we have implemented several strategies: 1) development of a brief video of “Making Your Wishes Known” that demonstrates the user-friendly nature of this online program to be shown to potential participants during initial recruitment; 2) employing a non-technical, user-friendly interface with audio and video enhancements; 3) designing the program at an 8\textsuperscript{th} grade reading level (and using a literacy test to screen for this); 4) providing an on-site research assistant for technical support; and 5) conducting study visits in a controlled research setting to ensure that the computer will work properly (i.e., configuration, internet access, etc.). See C2.2 and C2.5 for pilot data showing that that a wide range of patients find “Making Your Wishes Known” easy to use and helpful.

Burden of the protocol: Though participants must commit to 2-3 visits lasting 1-3 hours each, our prior work indicate that patients and family caregivers willingly participate in such studies and do not find it burdensome -- in part because they find significant value in both the process and the product. We also will provide parking vouchers and payment to participants, and will schedule appointments at their convenience.

Retention and follow-up: Because of the short interval between Study Visit 1 and 2, plus regular phone contact until Study Visit 3, we anticipate adequate retention to meet study goals. Over 3 years in our current ACS study, <10% of enrolled patients have dropped out. Additionally, we have found that participants enjoy speaking with the researchers and value the opportunity to provide updates on their condition and care.

Difficulty in knowing when the caregiver becomes a surrogate: Ideally, we would like to interview family caregivers soon after they have had to make decisions as a surrogate. The challenge is to know when the caregiver has made such decisions. We will obtain this information in two ways: 1) asking caregivers to contact the investigators as soon as possible after having made surrogate decisions for the patient (and providing caregivers study information on a magnetic card for their refrigerator); and 2) if caregivers do not contact us, we will learn of their surrogate decision-making at the next follow-up phone call —meaning that we expect no more than 8-12 weeks will elapse before we learn of it.

C8.4. Potential Selection Bias and Generalizability. To address potential selection bias, we will gather data from decliners to look for differences from participants. To enhance generalizability, we include 3 distinct patient populations with life-threatening illness, draw from urban and rural settings, and oversample minorities.

C8.5. Strategy to Manage High Risk Aspects of Work. Due to the serious nature of advance care planning, patients and/or family caregivers may experience emotional distress as a result of considering end-of-life preferences. Though this distress is unlikely to be compounded by the online Decision Aid or other aspects of the study, we will evaluate participants for moderate/severe depression, will monitor for increased distress during the study, and will refer distressed individuals to social services and/or a psychiatrist. Participants at each site will be provided with names and contact information for crisis intervention in the event that a participant experiences severe emotional distress outside of the study environment. Further, if a participant expresses suicidal ideation (item 9 of the BDI-II), the on-call psychiatrist at the study site will be paged to conduct a thorough psychological assessment. If the individual is considered a danger to herself or others, security personnel will transport that individual to the emergency department for immediate assessment. In our current ACS study, none of the 155 patients who have completed screening measures have required psychiatric or emergency services, and only 1 has been referred to social services due to emotional distress.

C9. Benchmarks for Success. This project will have succeeded if family caregivers in Group 4 (Decision Aid/Together) are better prepared for surrogate decision-making than those in the other groups, as measured by greater self-efficacy, less distress, and greater knowledge and understanding. If successful, future studies would examine how to integrate an effective ACP strategy into daily medical practice.
Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

The main purpose of this minimal risk study is to evaluate whether family caregivers of patients with life-threatening illnesses (advanced cancer, pulmonary disease, and congestive heart failure) are better prepared and have better experiences with surrogate decision-making when they engage in advance care planning (ACP) together with patients (versus patients engaging in ACP alone) and when they use an on-line decision aid for advance care planning (versus using standard ACP materials). In doing so, we will also examine interactions between these factors.

Using a 2 x 2 factorial design, 200 patient/caregiver dyads will be assigned to one of four groups: Group 1: Standard ACP/Alone, where the patient (but not caregiver) uses standard ACP materials to engage in ACP; Group 2: Decision Aid/Alone, where the patient uses the decision aid to engage in ACP; Group 3: Standard ACP/Together, where the patient and caregiver use standard ACP materials together; and Group 4: Decision Aid/Together, where the patient and caregiver use the decision aid together.

At Study Visit 1, patients and/or caregivers will engage in ACP using either standard materials or the decision aid. Four weeks later at Study Visit 2, patients and caregivers will independently complete hypothetical vignettes, and investigators will conduct in-person interviews with caregivers. Subsequently, caregivers will be interviewed by phone every 8-12 weeks until they report having made a surrogate medical decision for their loved one, after which caregivers (but not patients) will be asked to return for an in-person interview that will constitute Study Visit 3.

Participants will be recruited from Penn State Milton S. Hershey Medical Center in Hershey and Brigham and Women's Hospital (BWH) in Boston.

Patient inclusion criteria:
1) ≥18 years of age
2) Diagnosis of advanced cancer (Stage IV disease or having an estimated survival of ≤2 years) or severe congestive heart failure (Class III or Class IV as per New York Heart Assoc.) or severe lung disease (Stage III or Stage IV COPD by modified GOLD Spirometric Classification)\(^6\)
3) Able to read and understand English at an 8th grade level (word 26 on WRAT-3 reading subtest)
4) Neuro-cognitively able to engage in ACP (Mini Mental State Exam (MMSE) score >23)
5) Not more than moderately depressed (i.e., BDI-II score of <20/63).

Caregiver inclusion criteria:
1) ≥18 years of age
2) Identified by the patient as the family caregiver who will be the patient’s primary surrogate decision-maker (if non-cohabitant, must have in-person interaction with patient at least once weekly)
3) Able to read and understand English at an 8th grade level (word 26 on WRAT-3 reading subtest)
4) Neuro-cognitively able to engage in ACP (Mini Mental State Exam (MMSE) score >23)

b. Sources of Materials

Data will be collected from participants in the form of questionnaires, vignette exercises, a computer-based advance care planning program, telephone interviews, and in-person interviews.

The only identifying information to be included in the data set will be patient/caregiver zip code and county of residence. Only the study coordinator and project research assistant will have access to the identities and contact information of the participants throughout the study. The list connecting an individual with a study identification number will be available only to the study coordinator and research assistant, and kept in a locked file cabinet. When the study is complete, this list will be destroyed and the de-identified data set maintained indefinitely. The consent form with a participant’s signature will not contain any link to a subject’s
study identification number and will be stored separate of any study data.

c. Potential Risks

This is a minimal risk study, consisting primarily of in-person and telephone interviews and education. The education consists of having participants utilize a computer program and other forms of educational materials about advance care planning (ACP), which is the process of preparing for medical decision making in the event that an individual is unable to make decisions for him or herself. Due to the serious nature of advance care planning, patients and/or family caregivers may experience emotional distress as a result of considering end-of-life preferences. Though this distress is unlikely to be compounded by the computer-based decision aid or other aspects of the study, we will screen participants for moderate/severe depression, will monitor for increased distress during the study, and will refer distressed individuals to social services and/or a psychiatrist. Participants at each site will be provided with names and contact information for crises intervention in the event that a participant experiences severe emotional distress. Further, if a participant expresses suicidal ideation (item 9 of the BDI-II), the on-call psychiatrist at the study site will be paged to conduct a thorough psychological assessment. If the individual is considered a danger to herself or others, security personnel will transport that individual to the emergency department for immediate assessment. We have used this mechanism in our current ACS-funded study where patients with advanced cancer use the ACP decision aid. Of the 155 patients who have completed screening measures in this study, 8 have screen-failed due to moderate/severe depression, 1 spoke with social services due to emotional distress, and none have required psychiatric or emergency services.

Though participants in our prior or ongoing studies have not found the computer program, questionnaires, and vignette exercise burdensome to complete, some individuals may experience fatigue. To address this, participants will be able to stop, rest, and resume when they are ready, as well as withdraw from the study at any point.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Patients: All patients at both study sites (Penn State Milton S. Hershey Medical Center (PSHMC) in Hershey and Brigham and Women’s Hospital (BWH) in Boston) who meet inclusion criteria will be eligible for screening. Potential patients will be identified by participating attending physicians, who will send a letter of introduction along with an addressed stamped envelope that patients can mail to the study coordinator to opt out of being contacted by a research team member. We expect to enroll 200 patients (plus 200 caregivers) into the study.

Patients who do not opt out will be contacted by the study coordinator and, if interested in participating, will be scheduled (along with their family caregiver) for a study visit (Study Visit 1). The study visit will be conducted in a private room in the General Clinical Research Center (GCRC). The research assistant will describe the purpose of the study, possible risks and benefits for participants, confidentiality of responses, the voluntary nature of the study, and the right to withdraw or refuse to participate. The patient will be provided an overview of the subject matter, including the time commitment and notification that some individuals may find the topics distressing. The research assistant will obtain written informed consent on the Institution’s approved consent form.

Family Caregivers: In this study, family caregivers are defined as family members or close personal friends who have at least weekly in-person interaction with the patient, and whom the patient identifies as the individual they wish to serve as their surrogate for medical decision-making. The research coordinator will speak separately with the caregiver to explain the project and discuss study expectations and eligibility. Interested patient/caregiver dyads then will be scheduled for a joint in-person appointment (Study Visit 1), where informed consent will be elicited and participants will be screened for eligibility. Specifically, the research assistant will describe the purpose of the study, possible risks and benefits for participants, confidentiality of responses, the voluntary nature of the study, and the right to withdraw or refuse to participate. The family caregiver will be provided an overview of the subject matter, including the time commitment and that some
individuals may find the topics distressing. The research assistant will obtain written informed consent on the Institution's approved consent form. After providing informed consent, participants will complete instruments for eligibility screening.

b. Protection Against Risk

If a participant tests positive for moderate/severe depression on the BDI-II, a social worker from the Department of Psychiatry will be paged to conduct a brief assessment and, as necessary, provide a referral for community outpatient care. If any participant expresses suicidal ideation (item 9 of the BDI-II), the on-call psychiatrist at the study site will be paged to conduct a thorough psychological assessment. If the individual is considered a danger to herself or others, security personnel will transport that individual to the emergency department for immediate assessment.

With prior notification about the nature of the subject matter and the option of individuals to decline participation, we expect that psychological distress during participation will be rare. However, if distress does occur, we will refer the individual to social services and/or a psychiatrist, as per standard practice at both study sites. Additionally, participants at each site will be provided with names and contact information for crisis intervention in the event that a participant experiences severe emotional distress outside of the study environment.

Confidentiality will be achieved by maintaining any personally identifying information separate from data sets. The study coordinator and research assistant need to know the name and contact information of subjects until the data collection is complete. However, the list that connects a participant with a study identification number will be available only to the study coordinator and research assistant and will be kept in a locked file cabinet in the study coordinator's office. When the study is complete, this list will be destroyed. The consent form with the participant's signature will not contain any link to a subject's study identification number, and will be stored separately from study data.

In the event that an adverse event occurs, the study coordinator will immediately contact the site Principal Investigator (Levi or Green in Hershey, or Lehmann in Boston). The responding individual will then take appropriate action to assure the participant's safety. Thereafter, PI Levi will provide written documentation of the event to the Penn State Milton S. Hershey Medical Center's Institutional Review Board (IRB), the NIH, and (as appropriate) the participant's treating provider and/or the BWH IRB. Further, an independent Data Safety and Monitoring Board has been established for this study to ensure the safety of participants (discussed in detail below).

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Patients may benefit by gaining knowledge about end-of-life issues and this may help them communicate their wishes for medical care in the event that they can no longer speak for themselves. Caregivers may benefit from increased awareness and communication about the patient's wishes, and this may ease the stress associated with surrogate decision-making. However, these cannot be considered of benefit to all participants in the study.

Society may benefit from the findings of this study as we learn optimal ways to educate people about advance care planning and assist family caregivers in their role as surrogate decision-makers. This information may ultimately be helpful in increasing the quality and availability of advance care planning.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The study may lead to a better understanding of optimal methods for educating people about the complex subject of advance care planning, and for creating effective mechanisms to accurately communicate their wishes for medical treatment in the event they cannot speak for themselves. In a world of increasing medical complexity, such interventions will be a great asset for family caregivers who are asked to speak for patients when they are no longer be able to make treatment decisions for themselves. These potential benefits outweigh the minimal risks associated with participation.
5. DATA AND SAFETY MONITORING PLAN

An independent Data Safety and Monitoring Board (DSMB) has been established for this study to ensure the safety of participants and the validity and integrity of the data. All DSMB members are external to the project: the DSMB Chair (Paula Milrone-Nuzzo, RN PhD http://www.hhdev.psu.edu/nurs/faculty/milonenuzzo.html) is a nurse researcher who is Dean of the College of Nursing and has extensive experience in data safety monitoring; the other members are Neal Thomas, MD MS, a physician researcher who is Coordinator of Penn State Milton S. Hershey Medical Center’s Conflict of Interest oversight group, and Deborah Davis, DSW, the Director of the Office of Diversity Inclusion & Employment Equity at the Penn State Milton S. Hershey Medical Center.

The DSMB will meet annually and whenever necessary to review any development that could affect participants' safety. The DSMB will review the research protocol and its implementation; evaluate the study progress, including participant recruitment, accrual and retention; assess data quality and maintenance of confidentiality; review adverse events; evaluate participant risk versus benefit; review new scientific developments that could impact participant safety or the ethics of the study; and may request interim analyses of outcome data (presented privately by the study biostatistician). Minutes of DSMB discussion will be included in the annual progress report to NIH and the IRB, and any adverse event immediately reported to the IRB, DSMB Chair, and the NIH.

The research team will meet every week to monitor the study, identify problems early, and respond quickly to the identified problems. All research team members have completed online human subject research and HIPAA training modules provided by Penn State Milton S. Hershey Medical Center. The PIs will also train study staff in confidentiality procedures and will periodically monitor staff to ensure that these procedures are followed. Data will be monitored frequently to allow us to promptly recognize and rectify problems.
INCLUSION OF WOMEN AND MINORITIES

Women and minorities will be included in this research. We expect no difficulties in recruiting women and expect them to represent at least 50% of the family caregivers. In our currently funded study of patients with advanced cancer, 42% of participants have been female. Additionally, regardless of the patient's gender, research shows that 2/3-3/4 of family caregivers are female (see C8.2 for references). Thus, women will be more than adequately represented in this research on family caregivers.

Though we have successfully recruited minorities in pilot studies, PSHMC's small minority population (<5% of patients seen) poses a challenge to recruiting substantial numbers of non-white participants at this site. For this reason, we have added a second study site in Boston, where they will exclusively recruit non-white participants. BWH has an electronic database that allows researchers to query by diagnosis and race/ethnicity, and we will use this in our screening at that site to oversample for ethnicity/race and stratify across the intervention arms. Under the supervision of Dr. Lehmann, BWH will recruit a total of 50 minority participants into the study, which will represent 25% of the overall study population.

In order to appeal to an ethnically and racially diverse audience, our advance care planning computer program includes characters and situations that represent adults from minority as well as majority populations.
**Targeted/Planned Enrollment Table**

This report format should NOT be used for data collection from study participants.

**Study Title:** Preparing Family Caregivers of Very Ill Patients for End-of-Life Decision-Making

**Total Planned Enrollment:** 200

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<tr>
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<td>25</td>
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<tr>
<td>Not Hispanic or Latino</td>
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<tr>
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**Racial Categories**

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<tr>
<td><strong>Racial Categories: Total of All Subjects</strong> *</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."
INCLUSION OF CHILDREN

Patient and caregiver participants ages 18-21 will be included, but individuals under age 18 will be excluded because the complexity of making end-of-life decisions for and by minors is beyond the scope of this proposal.
Multiple PI Leadership Plan

Due to the complexity of the project and complementary skills of the investigators, Michael J. Green, MD MS, and Benjamin H. Levi, MD PhD will have equal leadership on this project with responsibilities as outlined in the multiple-PI designation plan below. Drs. Green and Levi have worked closely together for many years, and have offices in a common suite in the Department of Humanities at Penn State College of Medicine. As such they communicate with each other daily in addition to planned project meetings. Drs. Green and Levi will share overall responsibility for the project, and together will provide oversight of the research program administration, recruitment, logistics, study procedures, data collection, data analysis, and publication of results. They also will ensure that the specific aims of the research project are completed in accordance with all Penn State College of Medicine Human Subjects Protection Office, DHHS, and NIH policies concerning both human subjects and scientific data.

The specific tasks of the project will be delegated as follows: Dr. Green will be responsible for fiscal and administrative management including budget management, communication with NIH, submission of annual reports, and oversight of all data entry and technology management (e.g., trouble-shooting with computer programs, etc.). He will also be responsible for training and supervision of study personnel. Dr. Levi will be responsible for operational management of recruitment, study visits, telephone interviews, and all institutional IRB submissions and communication. Decisions regarding study protocol, analysis, and publication will be made jointly by Drs. Green and Levi, with authorship assignments based on the relative contributions of the PIs and key personnel.

Drs. Green and Levi’s collaboration in creating and testing their decision aid for advance care planning is built on a shared decision-making model that does not readily lend itself to a single PI management plan. Their respective strengths in both research and project management combine to create a broader and more effective approach to study design, investigation, and problem-solving, compared to a more formal hierarchy of leadership.

Conflict Resolution: Drs. Green and Levi have a long track record of successful collaboration and the ability to resolve disputes and/or conflicts that arise in the course of their professional work. If a potential conflict develops that cannot be resolved with good faith efforts by Drs. Green and Levi, their Departmental Chair, Dr. Dan Shapiro (who is a clinical psychologist) will meet with them to help settle any dispute. However, if this fails to resolve the disagreement within thirty business days, then the matter will be referred for resolution to a senior Penn State administrator who has the authority to settle the disagreement but who is not directly involved in the disagreement.
References


Consortium Arrangement

If this grant application is funded, the Penn State University College of Medicine will enter into an agreement with The Brigham & Women’s Hospital, Inc. with Lisa Lehmann, MD, PhD as the consortium PI.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency’s consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

The cost reimbursable agreement will be administered by Research Accounting at Penn State University College of Medicine.
Letters of Support

1. Marie T. Nolan, PhD, RN, Professor, Chair, Department of Acute and Chronic Care School of Nursing, Johns Hopkins University, Baltimore, MD

2. Thomas P. Loughran, Jr, MD, Professor of Medicine and Director, Penn State Hershey Cancer Institute, Hershey, PA

3. Edwin K. Silverman, MD, PhD, Associate Professor of Medicine, Brigham and Women's Hospital, Boston, MA

4. Daniel J. DeAngelo, MD, PhD, Associate Professor of Medicine Clinical Director, Adult Leukemia Program, Harvard Medical School, Boston, MA

5. Myra J. Christopher, President and CEO, Center for Practical Bioethics, Kansas City, MO

6. Rebecca Jenkins, Administrative Manager, General Clinical Research Center, Penn State Hershey College of Medicine, Hershey, PA

7. Kevin F. Staveley-O'Carroll, MD, PhD, Associate Professor of Surgery, Microbiology & Immunology, Acting Chief, Division of Surgical Oncology, Penn State Hershey Cancer Institute, Hershey, PA

8. Salah Almokadem, MD, Assistant Professor of Medicine, Division of Hematology/Oncology, Penn State Hershey Cancer Institute, Hershey, PA

9. Rebecca Bascom, MD, MPH, Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Penn State Hershey Medical Center, Hershey, PA

10. John P. Boehmer, MD, Professor of Medicine and Director, Heart Failure Clinic, Penn State Hershey Medical Center Heart & Vascular Institute, Hershey, PA