<table>
<thead>
<tr>
<th><strong>Title:</strong></th>
<th>Multisite randomized controlled trial of continuing vs. discontinuing statins</th>
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<tr>
<td><strong>Protocol Number:</strong></td>
<td>PCRC11-01</td>
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<tr>
<td><strong>Sponsor</strong></td>
<td>National Institutes of Health / National Institute of Nursing Research</td>
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<td><strong>Grant number</strong></td>
<td>#1UC4NR12584-01</td>
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</table>
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Jean S. Kutner, MD, MSPH *(University of Colorado, Denver)* |
| **Lead Statistician** | Diane Fairclough, DrPH *(University of Colorado, Denver)* |
| **Coordinating Centers** | Duke University Medical Center  
University of Colorado, Denver |
| **Protocol Version Release Date:** | Version 3.0  
April 1, 2013 |
| **Revision History** |  
**Version 1.0** Original protocol approved, February 16, 2011  
**Version 1.1** Minor changes from protocol submitted with grant submission to clarify data collection time points and document database being used (DataTrak rather than REDCap), March 7, 2011  
**Version 1.2** Clarification on data collected from caregiver, and AE reporting and procedure clarification, April 19, 2011  
**Version 1.3** Changes in Federal guidelines in language and reporting requirements for suspected unexpected serious adverse reaction (SUSAR), unanticipated problem involving risks to subjects or others (Suspected UPIRTSO) incorporated into protocol September 6, 2011  
**Version 2.0** Inclusion of individuals who are cognitively impaired, April 11, 2012  
**Version 3.0** Changes to study size, primary endpoint, statistical considerations and minor administrative/editorial corrections, April 1, 2013 |
Protocol Synopsis

Background
Currently, over 80% of the population is expected to die of chronic life-limiting illnesses,\(^1\) predominant among which are the various manifestations of cardiovascular disease, cancer, dementia, and chronic lung disease. Patients with high cholesterol and those potentially at risk for atherosclerotic heart disease and stroke are often treated preventively with HMG Co-A reductase inhibitors (a.k.a., statins). Clinical trial evidence supports the use of statins for patients with hyperlipidemia and established ischemic heart disease to reduce risk of future cardiovascular events and mortality, and to reduce risk of future cardiovascular events in patients with multiple cardiac risk factors. Beneficial outcomes are evident in these trials after 3-6 years of treatment.\(^5\) Hence, statins are among the most prescribed medications in the world. In the United States, over 25% of Medicare beneficiaries take a statin medication.\(^1\) Statin medications are frequently continued until the patient can no longer eat or swallow at the end of life, because there are no evidence-based guidelines regarding when or how to discontinue medications for co-morbidities. The risks and costs vs. benefits of statins for palliative care patients, for whom prognosis is limited, remains a genuine clinical uncertainty. Meanwhile, medications for symptoms and other concerns accumulate as illness progresses,\(^3\) and therefore polypharmacy and compounding medication side effects are troublesome problems in the setting of advanced life-limiting illness.\(^4,5\) While multiple studies have demonstrated the benefit of long-term preventive statin use for patients at cardiovascular risk,\(^6-8\) other studies have supported the discontinuation of medications (specifically statins) in end-stage disease.\(^9,10\) A rational approach to medication discontinuation, specifically statin discontinuation, therefore has the potential to reduce patient burden, polypharmacy, and side effects, while also preserving healthcare resources for more beneficial interventions.

Study design
This protocol describes a multi-site randomized controlled trial of discontinuing vs. continuing statin medications in patients with advanced life-limiting illness. Eligible participants are adults with advanced life-limiting illness with an estimated prognosis of 1-6 months who are on statins for primary or secondary prevention of cardiovascular events. The primary outcome is survival within 60 days after enrollment; secondary outcomes address cardiovascular events, polypharmacy, medication adverse effects, quality of life (QOL), and measures of the patient’s health-related experience. The primary hypothesis is that discontinuing statins will not influence survival rates. Secondary hypotheses are that discontinuation of statins will not adversely affect cardiovascular events or overall QOL, but will improve statin-related symptoms and decrease polypharmacy.

Study objectives
Primary objective
• To determine, among patients with life-limiting illness, if there is a difference in the proportion who die within 60 days after enrollment between patients for whom statins are discontinued vs. patients who are maintained on the medication.

Secondary objectives
Secondary analyses will investigate the following outcomes:
• Overall survival (OS), as measured by time-to-death
• Important CVD events, as measured by time-to-first-important-event, consisting of:
  o Admission to a hospital for a reason related to CVD
  o Admission to an emergency department for a reason related to CVD
• Having undergone an invasive CV procedure
• Having been diagnosed with a new CV event
• Quality of Life (QOL), as measured by the McGill QOL Questionnaire (MQOLQ), specifically:
  o Overall QOL (part A question 1)
  o Physical QOL (part B questions 1–4)
  o Combined QOL over past 2 days (Part C questions 1–12)
• Symptoms, as measured by the Edmonton Symptom Assessment System (ESAS), specifically:
  o Combined score from the standard 9 questions (pain, fatigue, nausea, depression, anxiousness, drowsiness, appetite, well-being, and breathing)
  o Combined score from the additional 4 questions (muscle-related pain, weakness, headaches, and fever)
  o Combined score from all 13 questions asked
• Performance status, as measured by the Australia-Modified Karnofsky Performance Status scale (AKPS)
• Polypharmacy
• Satisfaction with care, as determined by likelihood to recommend
• Costs

Methods
Consenting participants will be randomized 1:1 to discontinue statins (intervention) vs. to continue on statins (control); groups will be stratified by study site and history of cardiovascular disease. Assignments will not be masked, as blinding would prevent evaluation of the impact of knowingly discontinuing the medication on psychological distress measures. The intervention group will discontinue their statins. The control group will continue on statins until those medications can no longer be administered or the primary treating physician/primary care provider determines that continuing on statins is no longer safe. Intervention adherence will be carefully monitored in both study groups. Extensive communication with treating physicians/primary care providers will be part of the recruitment procedures; each participant’s treating physician/primary care provider will be fully knowledgeable about the study at the time the participant is randomized. If at any time the study participant, the loved one of the study participant and/or the treating physician considers participation in the study to not be in the best interest of the study participant, any of these individuals can request withdrawal from the study.

Statistical analysis
All analysis will be performed using an Intent-to-Treat (ITT) approach. Three of the endpoints (the primary endpoint and the first two secondary endpoints listed above) will utilize a non-inferiority analyses with one-sided tests (alpha=0.05). The difference (d) that we wish to exclude in the non-inferiority hypotheses is 5%, 3 weeks and 2 weeks respectively. The remainder of the endpoints will be tested in a superiority analysis with two-sided tests (alpha=0.05).

The primary analysis used will be a comparison of the binary endpoint (died vs. not died) between study groups. Secondary endpoints include both overall survival as well as clinically adverse cardiovascular events in participants who discontinue vs. continue statins. These will be analyzed using a time-to-event analysis for both overall survival and the first event after randomization. Additional secondary endpoints also include patient-reported QOL, psychological distress (anxiety, depression), other symptoms, polypharmacy, cost, and likelihood to recommend. Analysis of the longitudinal data will be performed using a mixed effects model, with additional sensitivity analyses for the effect of nonrandom missing data using a joint model with time-to-death and performance status.
**Significance**

This study will fill a current knowledge gap that frequently impedes palliative care clinicians’ ability to provide evidence-based care: Should statins prescribed for preventive purposes be discontinued when prognosis is limited? It will therefore directly contribute important information relevant to clinical practice and, given the extent of statin use, has major implications for rational management of polypharmacy and national healthcare resource allocation. If this trial and its methodology prove successful, it will directly contribute important information relevant to clinical practice and, given the extent of statin use, has major implications for rational management of polypharmacy and national healthcare resource allocation. If this trial and its methodology prove successful, it will serve as the starting point of a research agenda to determine the benefits vs. risks and costs of discontinuing other medications in the end-of-life setting; many of these medications have high patient burden and high cost, so the aggregate impact of these studies on patients’ QOL and reallocation of healthcare investments towards more beneficial interventions could be substantial.

**Summary of Amendment to Version 2.0**

The mid-study modification of eligibility criteria to include cognitively impaired study participants will expand generalizability of study findings to the broader population of individuals with advanced illness. The prevalence of cognitive impairment near the end of life is high\(^\text{11}\), and may be due to progression of the underlying terminal illness or may be age-related. Exclusion of individuals with cognitive impairment from the study can differentially exclude older adults, the exact population to whom the results are intended to be most relevant.\(^\text{12, 13, 14}\) In order to represent the spectrum of individuals with advanced illness and assure that study findings are applicable to clinical practice, the study population was expanded to include people who are cognitively impaired.

**Summary of Amendment to Version 3.0**

The DSMB recommended changing our primary endpoint from overall survival (using time-to-event data, specifically time-to-death) to the proportion of deaths within 60 days of enrollment onto the study (a binary endpoint). The sample size was adjusted to 360 in order to accommodate the modified endpoint.
## Study Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>AKPS</td>
<td>Australia-modified Karnofsky Performance Status scale</td>
</tr>
<tr>
<td>AT</td>
<td>As Treated</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CRC</td>
<td>Clinical research coordinator</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CTCC</td>
<td>Clinical Trials Coordinating Center</td>
</tr>
<tr>
<td>DISC</td>
<td>Development and Informatics Service Center, University of Colorado – Denver</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>ESAS</td>
<td>Edmonton Symptom Assessment System</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent To Treat</td>
</tr>
<tr>
<td>KPI</td>
<td>Key performance indicator</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky Performance Status</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MQOLQ</td>
<td>McGill Quality of Life Questionnaire</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>PCRC</td>
<td>Palliative Care Research Cooperative</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>SPMSQ</td>
<td>Short Portable Mental Status Questionnaire</td>
</tr>
<tr>
<td>SSDI</td>
<td>Social Security Death Index</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
</tbody>
</table>
Study Calendar

To minimize participant burden, study measurements will be efficiently collected. Independent variables will be measured at baseline only, and variables potentially impacted by the intervention will be measured at baseline, weeks 2 and 4, and every 4 weeks thereafter until death or 6 months (Week 24). The exceptions are survival, health resource utilization (HRU), and performance status, which will be monitored weekly in Weeks 1-4, every other week from Week 4 until death or 6 months (Week 24) and then monthly until death or 1 year (Week 52).

<table>
<thead>
<tr>
<th>Data collected</th>
<th>Baseline (Day 0 – 2) (in person)</th>
<th>Weekly, weeks 1-4; Even weeks, weeks 5-24 or death (by telephone)</th>
<th>Even weeks, week 2-4; Every 4 weeks, weeks 5-24 or death (by telephone)</th>
<th>Monthly, weeks 25-52 or death (by telephone)</th>
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<tr>
<td>Comorbid illness</td>
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<td></td>
<td></td>
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<tr>
<td>Smoking history</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Recent labs</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Information on statin taken</td>
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<td>Potential concerns related to medication discontinuation</td>
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<tr>
<td>Insurance status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SPMSQ</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKPS¹</td>
<td>X X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Survival¹</td>
<td>X X X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Enrolled in hospice (y/n)</td>
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<tr>
<td>Receiving palliative care (y/n)</td>
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<td></td>
<td></td>
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<tr>
<td>MQOLQ</td>
<td>X X X</td>
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<td></td>
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<tr>
<td>ESAS</td>
<td>X X X</td>
<td></td>
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<td></td>
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<tr>
<td>Likelihood to recommend</td>
<td>X X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence to study intervention</td>
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<td></td>
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</tr>
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<td>Non-statin medications</td>
<td>X X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health resource utilization (hospital admissions, etc.)</td>
<td>X</td>
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</tbody>
</table>

¹monitored weekly for Weeks 1-4, every other week for Weeks 6-24, (i.e., 6 months). After 6 months, survival, AKPS and health resource utilization will be monitored until death or 1 year (Week 52) via monthly phone calls made by the Clinical Research Coordinator.

²Costs will be calculated from medication (including statin) and health resource utilization information using standardized reimbursement rates.
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## 1 Introduction

### 1.1 Polypharmacy in patients nearing the end of life

Patients in the palliative phase of medical care often continue to take multiple medications. One study, in a population of cancer patients over age 65 and hospitalized at a major cancer center, reported an average of 5.1 medications taken per patient; 27% of these medications were nonprescription. Another study, conducted at an acute palliative care unit with average patient age of 64, reported that patients took an average of 6.7 medications at the time of admission and 10.5 medications during their stay. Symptom-specific medications are usually prescribed as disease advances; according to one study in the palliative care setting, on average 2.5 (95% confidence interval [CI], 2.2-2.9) more symptom-specific medications were prescribed as death approached, as compared with the number of medications at the time of referral to palliative care services.

As well as incurring potentially unnecessary patient burden and cost, polypharmacy poses a patient safety concern, with accumulating side effects and toxicities. Patients in palliative care, given their underlying illnesses, may be at heightened risk for drug interactions when taking multiple medications. For drug interactions of all types, incidence of interactions is estimated to be 3-5% in patients taking small numbers of medications, but 20% in hospitalized patients who are taking 10 to 20 drugs. In the palliative care setting, many patients present with cancer and are elderly – both conditions that make drug interactions even more likely. A study of risk in the elderly population found that the number of adverse drug reactions decreased from 24% to 7% when the average number of drugs was decreased by one medication.

### 1.2 Use of statin medications and potential impact of change

Statins are among the most prescribed medications in the world; they are also commonplace among patients receiving palliative care. Given that >80% of individuals will die of a chronic life-limiting illness, and that >25% of Medicare beneficiaries are on a statin, a rational approach to medication discontinuation in this population has the potential to reduce patient burden and conserve healthcare resources for more meaningful interventions.

### 1.3 Statin continuation/discontinuation in patients with advanced disease

The risks and costs vs. benefits of statins for patients with advanced disease remains a genuine clinical uncertainty. Multiple studies support long-term statin use for prevention of non-fatal myocardial infarction (MI) and stroke in patients with cardiovascular risk (a.k.a., primary prevention), or for prevention of recurrent MI in those with known coronary artery disease (a.k.a., secondary prevention). Benefits of long-term statin use have been clearly shown for patients who live the 3-6 years required to observe meaningful risk reduction. Additional studies supporting the continued use of statins include observational studies which suggest that survivors of acute MI whose statins are discontinued may have higher one-year mortality than MI survivors who were never prescribed statins either pre or post MI. This could be attributed to a biological rebound or a risk-treatment mismatch, in which treatment is withdrawn from the very ill patients who need the treatment the most. However, in this study patients who discontinued statins also had higher rates of discontinuation of other cardioprotective medications.

An enlarging literature, predominantly published in palliative care journals, supports the discontinuation of statins (and other medications) in patients with advanced life-limiting illness. In 2005, Vollrath et al. proposed that statins be discontinued in this setting, given the increased risk of adverse side effects and little evidence of benefit. In the intervening five years, this clinical question has not been answered. Stevenson, Currow, Abernethy, and colleagues highlighted that as patients near death the number of medications needed to treat soars while the number needed to harm plummets; however, data are not available to quantify these trends.
The challenge of polypharmacy in the palliative care population looms as a major concern, as previously described.

Statins are not without significant patient burden. Up to 8% of patients taking statins report gastrointestinal side effects such as nausea, vomiting, and abdominal pain. The most serious adverse effect is myopathy (from mild myalgia [1-7%] to rhabdomyolysis [0-0.005%]) which is more common in patients who are older and who have metabolic disturbances, renal and hepatic compromise, or polypharmacy – factors characteristic of the palliative care population. For patients with life-limiting conditions who take statins, the balance of medication efficacy vs. burden remains unclear and widely debated.

Finally, the psychological impact of using or discontinuing statin medications in the setting of advanced life-limiting illness is unknown. Patients may feel relief when not taking as many tablets, anticipating the potential for fewer side effects, and paying less medication costs. Conversely, there may be increased distress and anxiety when discontinuing a medication that a person was told he/she would be “taking for the rest of your life,” as the realization that life is limited sets in. Both potential scenarios should be monitored.

2 Study objectives

2.1 Primary objective

• To determine if there is a difference in survival rate at 60 days after enrollment between (a) patients with advanced life-limiting illness for whom statins are discontinued, and (b) patients with advanced life-limiting illness who are maintained on statins.

2.2 Secondary objectives

The objective for all secondary outcomes is to investigate differences in the outcome between patients who discontinue statins vs. patients who continue to take statin medications (all patients will have life-limiting illness).

Secondary analyses will investigate the following outcomes:

• Overall survival (OS), as measured by time-to-death
• Important CVD events, as measured by time-to-first-important-event, consisting of:
  o Admission to a hospital for a reason related to CVD
  o Admission to an emergency department for a reason related to CVD
  o Having undergone an invasive CV procedure
  o Having been diagnosed with a new CV event
• Quality of Life (QOL), as measured by the McGill QOL Questionnaire (MQOLQ), specifically:
  o Overall QOL (part A question 1)
  o Physical QOL (part B questions 1–4)
  o Combined QOL over past 2 days (Part C questions 1–12)
• Symptoms, as measured by the Edmonton Symptom Assessment System (ESAS), specifically:
  o Combined score from the standard 9 questions (pain, fatigue, nausea, depression, anxiousness, drowsiness, appetite, well-being, and breathing)
  o Combined score from the additional 4 questions (muscle-related pain, weakness, headaches, and fever)
  o Combined score from all 13 questions asked
• Performance status, as measured by the Australia-Modified Karnofsky Performance Status scale (AKPS)
• Polypharmacy
• Satisfaction with care, as determined by likelihood to recommend
• Costs

3. Study Design

3.1 Overview of design
This is a multi-site randomized controlled trial. Eligible participants are adults with a life-limiting illness who are on statins for primary or secondary prevention of cardiovascular events. The primary outcome is the proportion who die within 60 days; secondary outcomes include time to clinically adverse cardiovascular events, performance status, health-related QOL, anxiety and depression, symptoms, likelihood to recommend, polypharmacy, and cost. The hypothesis is that discontinuing statins will not influence survival in the first 60 days, cardiovascular events or overall QOL, but will improve statin-related symptoms and polypharmacy. Independent variables will be measured at baseline only, and variables potentially impacted by the intervention will be measured at baseline, weeks 2 and 4, and every 4 weeks thereafter until death or 6 months (Week 24). The exceptions are survival, health resource utilization (HRU), and performance status, which will be monitored weekly in Weeks 1-4, every other week from Week 4 until death or 6 months (Week 24) and then monthly until death or one year (Week 52). Baseline data collection will be in-person; all other follow-up data will be obtained by telephone unless otherwise specified. Should a participant survive to one year and he/she is in the intervention group, his/her treating physician will be contacted to determine if statin usage should resume. The anticipated sample size across all data collection is at least 360 participants.

3.2 Eligibility (Participants)
Patients enrolled in this randomized controlled trial must satisfy the following inclusion criteria:
• age ≥18 years old;
• have an advanced life-limiting illness;
• have a life expectancy of >1 month, AND patient exhibits declining functional status, defined as a reduction in Australia-modified Karnofsky Performance Status scale (AKPS)\textsuperscript{23} score to <80% in the previous 3 months;\textsuperscript{1}
• be on a statin medication for primary or secondary prevention of cardiovascular disease for ≥3 months;
• have adequately intact cognitive status to provide informed consent and complete the baseline assessment, as evidenced by a Short Portable Mental Status Questionnaire (SPMSQ)\textsuperscript{24} score of ≥6; OR, in the setting of impaired cognition precluding informed consent, have a legally authorized representative (LAR) who is willing and able to provide proxy consent and study data related to the person with advanced life-limiting illness;
• provide informed consent OR have LAR who provides informed consent; and, speak and read English at or above a grade 5 level (per patient or caregiver report).

Patients who meet any of the following exclusion criteria will not be eligible for the study:

\textsuperscript{1} This performance status level is specified to ensure that we capture a population that is likely to live at least one month but less than six, so that patients can provide the scheduled assessments while also being hospice-eligible.
• primary treating physician/care provider estimates their life expectancy as < 1 month;
• under the care of a primary treating physician/primary care provider who is unwilling to have the patient enrolled;
• not consenting;
• having known active cardiovascular disease or sufficient risk of active cardiovascular disease to require ongoing therapy with statin drugs, in the opinion of the treating physician; OR,
• exhibiting obvious symptoms of myositis, known liver function test (LFT) abnormalities of >2.5x the upper limit of normal (ULN), known creatine kinase (CK) abnormalities of >2.5x ULN, or other contraindications to continuing statins, in the opinion of the treating physician.

3.3 Setting and recruitment of participants

Participants will be recruited through the academic and community-based clinical sites participating in the Palliative Care Research Cooperative Group (PCRC). Each Site will minimally include a Site Principal Investigator (PI) and Clinical Research Coordinator (CRC) or similar staff member capable of enrolling in and conducting the study.

The total enrollment target is at least 360 patients; an enrollment target for each Site is assigned based on each institution’s potentially eligible population and expected ability to recruit, as reflected in prior research experience in the local population. The study may continue enrolling above 360 patients at the discretion of the Data Safety Monitoring Board in order to gain additional data for secondary analyses; secondary analyses are critical to put the primary study endpoint into clinical context.

Participants can be inpatients or outpatients; outpatient participation can be through clinics or in the home.

The Co-PI and staff at the Clinical Trials Coordinating Center (Duke) will develop study-specific recruitment strategies in consultation with Site PIs and staff, and will train Sites, develop and monitor recruitment metrics across the PCRC, and support staff at local Sites. The Site CRC will lead recruitment efforts at the local site, in consultation with the Site PI. Site CRCs and other study staff will attend an introductory training program covering research-related communication, ethics, recruitment planning and implementation, and social marketing. Screening and recruitment algorithms will be developed for each site, delineating expected processes and highlighting potential hurdles so that effective solutions can be developed. Key messages for the recruitment visit, supporting study diagrams, recruitment scripts, strategies for working with bereaved family members, documented history of cardiovascular disease, and simplified consent language will be developed. Tools will be practiced through role plays; refresher role plays will be repeated periodically during the study to ensure quality and consistency. Regularly scheduled CRC teleconferences will enable discussion of recruitment and enrollment procedures, sharing positive and negative experiences, and offering constructive advice to assist sites in overcoming recruitment hurdles. Recruitment metrics (a.k.a., Key Performance Indicators [KPIs]) will be monitored on a regular basis and will include screening, eligibility, randomization, study completion, and study withdrawal rates; progress will be presented to all Site PIs and staff. If a study site should encounter particular difficulty with enrollment, the team from the Clinical Trials Coordinating Center will conduct a site visit to review obstacles and devise solutions.

Each Site PI will interface with local stakeholders (e.g., oncologists, cardiologists, primary care providers, palliative care teams) to generate interest and buy-in. A case-finding method for each site, consistent with local and national privacy laws and IRB requirements, will be developed. For example, the CRC may screen referral lists for the hospice and palliative care programs daily for potential study participants and visit the outpatient...
oncology, pulmonary, geriatric, general medicine or palliative care clinics during periods when eligible patients are most likely to have appointments (e.g., lung cancer clinic). The CRC will have IRB-approved printed information sheets to distribute to clinicians during clinic hours; he/she will be reachable via pager or cell phone, will be available for discussions with patients at clinician request, and will be able to visit patients at home if needed.

During the recruitment visit, the CRC will review the consent documents in full, answer questions, and provide the potential participant (and family) or LAR (if cognitively impaired) time and space to make a considered decision. All signed consent documents will be maintained and stored in accordance with local IRB requirements; copies will also be filed in the study notebook according to the standard operating procedure (SOP). CRCs will prepare screening and recruitment logs that are forwarded to the Clinical Trials Coordinating Center and contribute to the KPI metrics reporting.

Participant recruitment will start as soon as (a) the protocol is approved by the Site IRB, and (b) site training has been completed.

### 3.4 Study procedures

#### 3.4.1 Randomization

On Day 0 (or within 2 days of enrollment/signing consent form), after completion of baseline assessment, consenting participants will be randomized 1:1 to continue on statins (control group) vs. to discontinue statins (intervention group), stratified by site, documented history of cardiovascular disease, and cognitive status, i.e. Cognitively impaired vs (SPMSQ) score of ≥6). Random block sizes will be used in each stratum; random allocation assignment will be computer-generated. Once a patient or LAR has formally consented to participate and provided baseline data, the CRC will access the central web-based randomization service for intervention allocation. Because we aim to study the effects of medication cessation on patients’ mental health and perceived QOL, we will not blind patients to the assignment; masking randomization by giving patients in the intervention arm a placebo would prevent us from assessing the full impact on patients of discontinuing a statin medication in the real-world setting.

#### 3.4.2 Intervention

At the time of enrollment (Day 0), the CRC will complete the baseline assessment in person, interviewing the patient in the hospital, home, or clinic, as appropriate for the individual participant. If the patient is cognitively impaired, the CRC will obtain baseline study data from the caregiver/proxy (who may or may not be the LAR). Home visits are a standard part of the hospice and palliative care culture, and will be used for study consent, enrollment and initial data collection to avoid participant burden. The baseline visit can be combined with the consenting and randomization visit, provided that consent is signed and the respondent is not overly tired. Next, the CRC will work with the patient (or caregiver/proxy) and treating physician/primary care provider to ensure that the statin medication is appropriately continued or discontinued (regardless of inpatient of outpatient setting) as per randomization allocation. CRCs will conduct follow-up by phone, as required (see section 3.4.3).

The intervention group will discontinue their statins. The control group will continue on statins until (a) those medications can no longer be administered, or (b) the participant’s primary treating physician/primary care provider judges the statin to be unsafe. Adherence will be carefully monitored. Extensive communication with treating physicians/primary care providers will be part of the recruitment procedures; the treating/p/primary care provider will be required to agree to eligibility; each participant’s treating physician/primary care provider will thus be fully knowledgeable about the study by the time the participant is randomized.
3.4.3 Order of study events

- Referral and eligibility screening: Days -14 to 0
- Consent: Day 0
- Baseline data collection & randomization: Day 0-2

Discontinue statin:
- Telephone assessment – survival, performance status, health resource utilization: Week 1*
- Telephone assessment – all outcome measures: Week 2
- Telephone assessment – survival, performance status, health resource utilization: Week 3
- Telephone assessment – all outcome measures: Week 4
- Telephone assessments – all outcome measures monthly; survival, performance status, health resource utilization every other week: Weeks 6-24

No change in statin:
- Telephone assessment – survival, performance status, health resource utilization: Week 1*
- Telephone assessment – all outcome measures: Week 2
- Telephone assessment – survival, performance status, health resource utilization: Week 3
- Telephone assessment – all outcome measures: Week 4
- Telephone assessments – all outcome measures monthly; survival, performance status, health resource utilization every other week: Weeks 6-24

Study exit – 6 months (Week 24) or death
- if patient still alive at 24 weeks, survival, performance status and health resource utilization will be monitored through monthly telephone calls until death or 1 year.

*Data will be collected within a three-day window, e.g., Week 1 data may be collected from Day 6-8.

3.4.4 Participant burden/time

Participant burden due to extensive study assessments and questionnaires is a well-documented obstacle to palliative care research and a significant concern of the investigators. Study measurements are therefore intentionally focused on the trial’s specific aims; extraneous information will not be collected. Independent variables will be measured at baseline only. Those variables that may be impacted by the intervention (i.e., dependent variables) will be measured at baseline only, and variables potentially impacted by the intervention will be measured at baseline, weeks 2 and 4, and every 4 weeks thereafter until death or 6 months (Week 24). The exceptions are survival, health resource utilization (HRU), and performance status, which will be monitored weekly in Weeks 1-4, every other week from Week 4 until death or 6 months (Week 24) and then monthly until death or 6 months (Week 24) and then monthly until death.
death or 1 year (Week 52). All data collection except at baseline will be conducted by telephone. Beyond 6 months, we will make a monthly telephone call to monitor survival, performance status and health resource utilization through death or 1 year.

Data provided directly by patients or caregiver/proxy will be obtained by interview (in-person at baseline, by telephone at all other assessments). The patient (or caregiver/proxy) will have large-font versions of the case report forms (CRFs) to follow along at home. If, at any time, the patient is too tired or is otherwise not able to continue with a data collection session AND gives the CRC permission to collect data from a loved one at the time of study enrollment/consent, then objective data will be collected from a person close to the patient. No subjective data, such as data related to symptoms, depression, quality of life, or how a patient feels/thinks about his/her illness will be collected from a caregiver. In the case of a cognitively impaired study participant, only objective data (baseline medical information, medication use, intervention adherence, hospice and palliative care utilization, survival, health resource utilization, venous thromboembolism, pneumonia, performance status, and likelihood to recommend) will be collected from the caregiver/proxy at baseline and all future timepoints.

In palliative care clinical trials previously conducted by the Principal Investigators, participants (patients and caregivers) have expressed a sense of disappointment or loss when the study ends and their follow-up contact from the study staff is discontinued. To sustain this source of support to study participants, the CRC will offer to continue to make monthly telephone calls beyond the end of scheduled data collection.

### 3.5 Outcomes Assessment

#### 3.5.1 Assessment overview

The baseline assessment and longitudinal monitoring of survival, performance status, health resource utilization, quality of life, symptoms, medications, and adverse events will be completed by the CRC using standardized CRFs. The baseline assessment will preferably be completed on Day 0 (day of consenting and prior to randomization), but if this is not possible (e.g., due to participant exhaustion), baseline may occur somewhere between Days 0-4. Longitudinal assessments are timed according to the study schedule, within 1 day before or after the planned assessment day.

Participating patients will receive a study notebook that contains all study surveys in large font format; the CRC will have the same packet of surveys, and will have a script to talk the patient through provision of the relevant data. At data collection points, the CRC will call the participant to collect the information, completing each of the CRFs in paper version for subsequent entry into the study database. Data collected on the CRFs will subsequently be entered into a central database hosted on a secure server; previously tested quality assurance measures will be implemented centrally. One part of the CRF will remain at the local site; the other part will be sent to the central site for quality checking purposes.

The PCRC Statistical Center and Data Management (SCDM) group (University of Colorado) will conduct quality monitoring of site-level processes, and remediate when needed, in conjunction with the Clinical Trials Coordinating Center. This approach has worked successfully for other multi-site trials completed by Drs. Abernethy and Kutner, with <1% missing data due to lost forms.
3.5.2 Measures and instruments

At baseline assessment only, the following data will be collected from sources as indicated:

- **participant demographics** (e.g., age, gender, ethnicity, education). Source – medical records or patient/family caregiver/proxy.
- **co-morbid illnesses** with a focus on cardiovascular diseases and risk factors (e.g., hypertension, diabetes, family history, body mass index, stroke), recorded as yes/no for current presence/absence of the condition; a Charlson Comorbidity Index score will be calculated for each participant based on this information. Source – medical records and patient/caregiver/proxy.
- **smoking history** in pack years and current smoking status (ongoing or date stopped). Source – patient/caregiver/proxy, verbally asked and recorded by CRC.
- **most recent laboratory studies**: hemoglobin, creatinine, lipid panel, LFTs, and CK, with dates and reference ranges. Source – medical records reviewed for the past 6 months, with preference for laboratory tests performed within the 4 weeks prior to randomization.
- **statin**: name, dose, frequency, number of years, indication. Source – medical records.
- **cognition**, as measured by the Short Portable Mental Status Questionnaire (SPMSQ), a 10-item scale. Source – patient-completed survey.
- **insurance status**, utilizing the Agency for Healthcare Research and Quality (AHRQ) categorization. Source – administrative records.
- **potential concerns related to medication discontinuation**, Questionnaire developed for this study (and future studies) based upon possible perceptions regarding discontinuation of medications, among patients nearing the end of life. Source – patient.

The following data will be collected at baseline and follow-up assessments, using the instruments indicated. The order of patient reported measures will be the MQOLQ, then ESAS, then willingness to recommend.

1. **Survival** (death rate at 60 days and time to death), measured as the proportion surviving at 60 days after enrollment (Day 0) in each arm and the time from the date enrolled (Day 0) to date of death. Source – proxy or caregiver report, death certificate. Note that safety, including changes in survival, will be carefully monitored by the Data Safety Monitoring Board (DSMB). Cause of death will be obtained from death certificate data and classified as cardiovascular, non-cardiovascular, or unknown. Cardiovascular causes of death will be closely monitored.

2. **Performance status**, as measured on the Australia-modified Karnofsky Performance Status scale (AKPS). The AKPS adapts the original Karnofsky Performance Status (KPS) to accommodate for varied inpatient and community palliative care settings. Drs. Abernethy and Currow previously compared the AKPS, KPS, and other scales during 1,600 time points for 275 palliative care patients over 21 months; the AKPS had the highest face validity and was most predictive of survival, especially at the lower ranges of the scale. Recently, Drs. Abernethy and Bull confirmed these findings in a community-based sample of >1,000 palliative care and hospice patients (unpublished). Source – patient/caregiver/proxy, to be obtained by the CRC, recorded upon assessment and questioning; CRCs will be specifically trained in using the scale in the context of a telephone interview.

3. **Health resource utilization**, including hospitalizations, emergency department presentations, cardiovascular procedures, new cardiovascular events, venous thromboembolism, and pneumonia. Information will include reason for hospitalization, number of days in the hospital, individual emergency department visits, and descriptions of each cardiovascular procedure. Source – patient/caregiver/proxy report.
4. **Health-related Quality of Life**, measured by the McGill Quality of Life Questionnaire (MQOLQ).\(^{29-32}\) The MQOLQ is specifically designed for a palliative care population, measuring whole-person concerns magnified by advanced life-limiting illness. It is short, reliable, repeatable, and can be used to determine changes in QOL of groups. Drs. Abernethy, Kutner, and other Site PIs have extensive experience using the MQOLQ; Dr. Fairclough has previously analyzed studies that incorporate it. The 18 questions are answered in reference to the prior two days. Variables include the 0-10 global QOL assessment and the 4 individual subscales of the MQOLQ - physical symptoms, psychological, existential, and support. The psychological subscale includes two questions that assess depression (depression, sad) and two questions that assess anxiety (nervous or worried, afraid of the future). At the end of the MQOLQ assessment, the CRC will give the patient the option of describing, in his/her own words, his/her personal experience of symptoms and quality of life. Based on the MQOLQ Part D (qualitative portion), this question will be carefully worded; answers will be transcribed by the CRC and scanned as PDF documents for possible future analyses. Source – patient-completed survey. Quality of life will NOT be obtained from caregiver/proxy respondents.

5. **Symptoms**, including some potentially statin-related symptoms, will be monitored using the Edmonton Symptom Assessment Scale (ESAS),\(^{33,34}\) which incorporates nine symptom items measured on 0-10 numerical rating scales (NRS). The ESAS will be supplemented with questions that focus on additional statin-related side effects (i.e., rash, muscle-related pain, muscle weakness, headaches, fever; nausea, a common statin symptom, is included in the original nine items from the ESAS. All will be measured on similar NRS scales as presented on the ESAS. The ESAS is repeatable and can measure change over time of individual items. Source – patient-completed survey. Symptom data will NOT be obtained from caregiver/proxy respondents.

6. **Likelihood to recommend** will be measured as an indicator of patient satisfaction, which focuses more on the specific intervention being studied than do typical satisfaction questionnaires. This single-item survey asks “Would you recommend discontinuation of statin medications to other patients with advanced illness who are receiving palliative or hospice care?”\(^{35}\) Source – patient-completed survey. When the patient is unable to respond, the caregiver/proxy can answer this question; the respondent will be recorded on the CRF.

7. **Adherence to study intervention**. Patients in both study arms will be followed for medication use and adherence to the designated regimen. Source – patient/caregiver/proxy, verbally asked and recorded by CRC.

8. **Non-statin medications** (name, continuous or as-needed); polypharmacy will be quantified as the number of medications administered daily. Secondary assessments of polypharmacy will include number of as-needed (a.k.a., “prn”) medications taken on >50% of days and the total number of prn medications prescribed. Source – concomitant medication forms and patient/caregiver/proxy.

9. **Adverse cardiovascular events** (AEs) monitored will include hospital admissions, emergency department visits, and invasive procedures specifically for new cardiovascular events. Source – patient/caregiver/proxy and/or medical records.

10. **Enrolled in hospice** (yes/no). Source – patient/caregiver/proxy, verbally asked and recorded by CRC.

11. **Receiving palliative care** (yes/no). Source – patient/caregiver/proxy, verbally asked and recorded by CRC.

12. **Costs**: Statin medication costs will be estimated by the Average Wholesale Price available in the most recent version of the *Red Book*. Hospitalization, emergency department and cardiovascular procedure costs will be assessed by using averages (on a per day or unit basis) as calculated by the Healthcare Cost and Utilization Project sponsored by the AHRQ.
3.6 Discontinuation of the Protocol

3.6.1 Participant discontinuation
Patients (or their Legally Authorized Representative (LAR) in the case of cognitively impaired participants) may discontinue their participation in this study at any time. If a participant/LAR chooses to discontinue, we will solicit reasons for his/her exiting the study via a brief open-ended interview conducted either in-person or via telephone by a CRC. We will record whether the patient/LAR is withdrawing from the data collection telephone calls, from having information obtained from their medical record, or both; data will be recorded, unless the patient/LAR refuses to have the reason for study withdrawal to be documented. We will assure the withdrawing participant/LAR that he/she may decline to participate in any further way without any repercussions whatsoever for his/her treatment or care.

Either the participant’s treating physician/primary care provider or the site investigator may recommend that the patient discontinue the study at any time. If this occurs, we will ask the treating physician/primary care provider if the patient may participate in evaluations for survival, health resource utilization, and performance status. We will continue evaluation unless the treating physician/primary care provider objects or the patient expresses a desire to discontinue providing this data.

Loved ones/caregivers of study participants will be encouraged to contact the treating physician and advocate on behalf of the patient if he/she feels that it is not in the patient’s best interest to continue study participation.

If the patient participant is still alive after 12 months on the trial, their participation in the study will be discontinued. The treating physician/primary care provider will be notified. If the patient’s statin medication had been discontinued, the treating physician/primary care provider can elect to resume the statin. Data will not be collected after 12 months.

3.6.2 Study discontinuation
The PCRC Steering Committee and the DSMB will have the right to discontinue the study in its entirety at any time. Reasons for terminating the study may include but are not limited to the following:

- patient safety concern; or
- failure to follow the study protocol.

3.6.3 Site discontinuation
The Site PIs, overall study Co-PIs, PCRC Steering Committee, DSMB, and/or IRB may terminate the study at a particular site at any time for any of the following reasons.

- unsatisfactory participant enrollment;
- patient safety concern;
- inaccurate or incomplete recording of data; or
- failure to follow the study protocol.
4  Statistical Considerations

4.1  Analysis Plan
All analyses will be performed using an Intent-to-Treat (ITT) approach. Three of the endpoints (the primary endpoint and the first two secondary endpoints listed above) will utilize a non-inferiority analyses with one-sided tests (alpha=0.05). The difference (d) that we wish to exclude in the non-inferiority hypotheses is 5%, 3 weeks and 2 weeks respectively. The remainder of the endpoints will be tested in a superiority analysis with two-sided tests (alpha=0.05).

4.1.1  Primary objective
The primary endpoint, demonstrating safety, is the proportion surviving at 60 days after enrollment in each study intervention arm. The analysis used will be a comparison of the binary endpoint (died vs. not died within 60 days of enrollment) between study groups, and will be tested using a 1-sided test with a type 1 error rate of 0.05 and the difference that we wish to exclude in the non-inferiority analysis is 5%.

4.1.2  Secondary objectives
Secondary analyses will investigate the following outcomes:
- Overall survival (OS), as measured by time-to-death
- Important CVD events, as measured by time-to-first-important-event, consisting of:
  - Admission to a hospital for a reason related to CVD
  - Admission to an emergency department for a reason related to CVD
  - Having undergone an invasive CV procedure
  - Having been diagnosed with a new CV event
- Quality of Life (QOL), as measured by the McGill QOL Questionnaire (MQOLQ), specifically:
  - Overall QOL (part A question 1)
  - Physical QOL (part B questions 1–4)
  - Combined QOL over past 2 days (Part C questions 1–12)
- Symptoms, as measured by the Edmonton Symptom Assessment System (ESAS), specifically:
  - Combined score from the standard 9 questions (pain, fatigue, nausea, depression, anxiousness, drowsiness, appetite, well-being, and breathing)
  - Combined score from the additional 4 questions (muscle-related pain, weakness, headaches, and fever)
  - Combined score from all 13 questions asked
- Performance status, as measured by the Australia-Modified Karnofsky Performance Status scale (AKPS)
- Polypharmacy
- Satisfaction with care, as determined by likelihood to recommend
- Costs

The first two secondary analyses listed above both have time-to-event (TTE) outcomes. These two analyses will use the non-parametric log-rank test to compare the TTE differences between the 2 study groups. A 1-sided test using $\alpha = 0.05$ will be performed with corresponding confidence intervals that will be used in the non-inferiority tests for the differences of 3 and 2 weeks respectively. Sensitivity analyses will also be performed. These analyses will be performed using Cox regression, incorporating the actual use of statins as time-varying
covariates. These sensitivity analyses will first be performed using the ITT approach, and then performed again using an As-Treated (AT) approach in order to be able to examine differences between the 2 approaches.

If there are significant differences in the composite measure of significant cardiovascular events, the time to each of the four components will be presented descriptively.

These remaining longitudinal endpoints will be tested using a 2-sided test with a type 1 error rate of 0.05. Analysis of the longitudinal data will be performed using a mixed effects model, with additional sensitivity analyses for the effect of nonrandom missing data using a joint model with time-to-death and AKPS.

### 4.2 Sample Size Justification

The goal of the primary analysis is to ensure that discontinuation of statins does not present a safety concern. This endpoint is measured as the proportion of patients who die within 60 days from enrollment. Based on preliminary pooled (i.e. blinded) data from the trial, the event rate is approximately 21%. With a total sample size of 360 patients randomized into the 2 study arms (180 patients per arm), the study would have 80% power to detect a difference in proportion of deaths of 12% (15% vs. 27%). We recognize that this study may be underpowered to detect a clear difference between the two interventions if one exists unless the difference is greater than 12%. That being said, a resizing calculation conducted in collaboration with the DSMB at an interim timepoint demonstrated that a non-inferiority design with adequate power to demonstrate a difference of 2% or less would require over 32,000 patients and would be infeasible. Hence, the sample size goals were adjusted and secondary analyses will be used to put the primary outcome results into context.

For the secondary longitudinal endpoints, we would have at least 80% power to detect effect sizes of 0.32 or larger (between a small and moderate effect) after accounting for missing assessments due to death/dropout (50% by week 12).

### 5 Data Management

#### 5.1 Data Management

The work of Dilts and colleagues highlights the importance of forms development and data management to efficient study conduct and completion; hence, the PCRC will focus on data forms (see above), databases, data management, and quality checks. Data management will be centralized at the Statistical Center/Data Management Office (SCDM). We will use a combination of centralized and decentralized data entry that minimizes burden at sites but allows timely monitoring of study performance.

**Trial Activation and Site Participation** – The SCDM will require documentation of IRB approval for each participating site including the date of expiration and the approved number of subjects. Enrollment, randomization and submission of data will require a current approval. Monthly reports will be used to track actual versus targeted accrual.

Each site will receive a specially prepared notebook detailing all data management procedures. Study data will be collected on two-part forms. After completed forms undergo site quality control procedures, data from the top part will be entered into a relational database residing in a password-protected directory on a secure institutional server, and then forwarded (within 1 week) to the SCDM Office. Standardized electronic data
validation checks will be developed using data entry discrepancy flags, programmed query rules, and, in certain cases, external rules using SAS code. The second part will be retained at the site for local documentation.

Once information is received by the SCDM Office, forms will be checked for completeness and readability. Questions or corrections will be addressed to individual sites for resolution. Following this edit check, the forms will be stored in a secure location; greater than 10% of the study data (with a minimum of four subjects per site) will be double-entered by the SCDM Office and checked for discrepancies against local entries. Discrepancies will be communicated by the SCDM Project Manager to each site’s CRC. Determination of correct information will be obtained, corrections will be made on the paper CRFs and/or in the electronic data capture system, and revised documents will be sent by the site CRC and stored at the SCDM office. Double data entry will be performed for all key variables (outcome variables, demographics, adverse events, non-compliance with randomization assignment, and study withdrawal), where error rates are larger than 1% to ensure data accuracy.

Monthly reports (in aggregate and by site) will be generated summarizing accrual, completeness of follow-up, and data quality. A regularly run program will check for missing data and perform other data checks as part of the query rules; queries will be generated as a part of data clarification forms that will be sent electronically to the sites. Sites will review the data clarification forms, make appropriate clarifications and corrections, and send copies of the corrected forms to the coordinating site. A query will remain open until completely resolved.

5.2 Data Storage and Confidentiality

Study data will be collected using the CRFs and entered on-site into the study database using electronic data capture by each site’s CRC. The study database complies with current FDA data security standards, and provides real-time data entry validation (e.g. for data types and range checks), and provides audit trails documenting any changes or corrections of the study data. In order to enter the data, the CRC will log into the Internet, then log into a secure portal with a username and password and enter the data directly into the database.

The database is hosted by the Colorado Prevention Center (CPC), and is HIPAA-compliant. Explicit identifying information (e.g., participant’s name and contact information) will be recorded on separate forms and will NOT be sent to the SCDM Office; these forms will be maintained locally at each site in a secure location. Study monitors will review the forms at the site to ensure local documentation is compliant and complete.

5.3 Data Safety and Monitoring

5.3.1 Data Safety and Monitoring Board (DSMB)

A DSMB will be formed to ensure safety and provide guidance, with the input of the NIH. The DSMB will comprise four expert members with relevant experience; at least one member will be a clinical trials statistician. Members will be appointed through joint agreement between the study Co-PIs, Co-investigators, and the NIH. The Committee will develop an explicit set of expectations and guidelines during the first meeting and follow these guidelines for all of the monitored period; these guidelines will follow the DSMB requirements of the NIH. Expected tasks include: safety monitoring for protection of participants; monitor trial progress for data quality, enrollment procedures and protocol compliance; evaluate that the risk/benefit ratio is not altered to the detriment of the subjects; conduct appropriate internal monitoring of adverse events and outcomes; ensure confidentiality; make recommendations for continuation, termination or modification; ensure any real or perceived conflict of interest issues are addressed.
The Co-PIs will continuously monitor and tabulate adverse events and provide reports to the DSMB and to the relevant IRBs.

5.3.2 Site visits/support

As an additional protection to human subjects, sites will be visited by a PCRC study staff member who will visit each site at least once during the conduct of the trial. The PCRC priorities are to assure that (a) the study is conducted in an ethical manner consistent with applicable federal regulations, local IRB specifications and DSMB advice, and (b) patients are receiving safe care within the context of the study. The PCRC will work together with the sites to ensure that study forms are complete and to rectify local data collection problems. The PCRC will assist with oversight of study screening and recruitment procedures and metrics, supporting sites as needed. The PCRC will also work with local staff at each site, to coordinate external supplemental monitoring as available through that site’s protocol office.

6 Quality Control

6.1 Adherence to Protocol

Adherence to the protocol will be monitored by the PCRC and reported to the Co-PIs, with additional IRB and DSMB reports when appropriate. Protocol deviations will be resolved within 72 hours of notice. All protocol deviations will be documented.

6.2 Study Progress

Key performance indicators (KPIs) will be used to monitor study progress and to ensure timely completion of the study. The main KPIs are:

KPIs Related to the Recruitment and Retention of Participants

- KPI 1: Eligibility rate, calculated as the proportion of screened patients who are eligible to participate;
- KPI 2: Enrollment rate, calculated as the proportion of eligible patients who are enrolled onto the study (where enrollment requires a participant to consent and are randomized);
- KPI 3: Withdrawal rate, calculated as proportion of patients who enroll but later withdraw.

KPIs Related to the Loss of Study Data

- KPI 4: Baseline data to Week 2 data collection rate, calculated as the proportion of patients with baseline data (excluding those who died within 14 days for whom Week 2 data are completed);
- KPI 5: Baseline data to Week 4 data collection rate, calculated as the proportion of patients with baseline data excluding those who die within 28 days for whom Week 4 data are completed;
- KPI 6: Baseline data to final survival data collection rate, calculated as the proportion of patients with baseline data for whom final survival data (whether or not they died and if so, what the date of death was) are available.
Reports (in aggregate and by site) detailing KPIs, enrollment, completeness and accuracy of data form completion, number of data queries, and adverse events and serious adverse events will be generated on a regular basis.

7 Human Subjects Research Concerns

7.1 Potential Risks to Human Subjects

This is a randomized comparative effectiveness study. Discontinuation of medications for medical comorbidities as death nears is a source of major debate. Statins are common medications (prescribed for >25% of Medicare beneficiaries) and there is a substantial literature both supporting and advising against stopping these medications. As described above, some experts worry about an increased risk of death from cardiovascular events, while other experts argue that discontinuation of statins reduces side effect burden, polypharmacy, and cost. Actual clinical practice varies widely, and discontinuation of statins on enrollment in hospice is standard of care in many organizations. There is definite equipoise about best practice.

Overall, there is a potential increased risk of cardiovascular death if medication withdrawal proves harmful. In addition, there is risk of psychological distress if a person who has been taking a medication for a long period of time perceives the medication withdrawal as abandonment by the medical establishment. Finally, there is risk to participants due to loss of confidentiality of patient clinical data.

These issues are the same for patients with advanced illness who also are cognitively impaired. The risk of including this vulnerable population into the study is minimal, given that we will be collecting objective data (no subjective, patient-reported outcome data) from their caregiver/proxy who is already in a position to know about and make medical decisions on behalf of the patient.

7.2 Protection Against Risks

Patients or, for those who are cognitively impaired, his/her legally authorized representative (LAR) will be actively recruited for this trial; all patients who meet eligibility requirements will be approached by trained study personnel to participate. These study personnel will explain the study to prospective participants/LARs, including all possible risks and potential benefits, and will provide them with an opportunity to ask questions. Study personnel will be carefully trained in research ethics, respectful communication, and how to answer patient/family questions. All four criteria for assessing a potential study participant’s capacity (or LAR’s capacity) must be met (understanding, appreciation, reason, and expression of the choice to participate) in order to proceed with study consent. If, after complete consideration of the protocol, the patient/LAR wishes to participate, he/she will review and sign a written informed consent document. Potential risks from participating in the study are outlined in detail in the consent documentation. Description of these risks will be carefully scripted and role-played with study personnel, to ensure clarity in presentation. The informed consent process follows applicable Federal Regulations (21 CFR part 50, subpart B) Institutional Review Board (IRB) and International Conference on Harmonization (ICH) guidelines.

The study procedures include a number of steps intended to minimize risk to participants. We will closely monitor participant complaints and adverse events, including cardiovascular adverse events. An Event Classification Committee, comprising a subgroup of the investigators, will be created for this study. The purpose
of this committee will be to review all events potentially classified as adverse, determine which of these events are cardiovascular vs. noncardiovascular in origin, monitor and document all events (adverse or otherwise), and recommend events to be reported to the IRB. A DSMB will be consulted, and both survival and adverse events will be monitored (see Section 7.3, below). A professional Study Monitor will be on the central staff for the cooperative group (PCRC), and will review all site activities and ensure adherence to IRB and ICH guidelines. Best ethical practice is a core principle of the cooperative group.

The following steps will be taken to protect against loss of confidentiality. First, all study personnel and investigators will be required to participate in mandatory and ongoing educational programs concerning research ethics. These programs are available through the IRBs of both Coordinating Centers as well as at most of the study sites, and administration and credentialing are supported by the respective institutions. One of these programs must be completed by all members of the investigative team prior to IRB approval of the proposed work. Second, all data will be collected with strict attention to HIPAA guidelines and stored using HIPAA-compliant data management systems, allowing only password restricted access to limited designated key study personnel. Only aggregate results for the population studied will be released; no individual patient data will be released from the database. Any links between a unique ID and patient contact information that could be used for subsequent follow-up will be maintained in a separate, password-protected file or locked file cabinet that is maintained at each individual site and will not be released to study personnel at the Coordinating Center or Data Center.

### 7.3 Adverse Events

In accordance with applicable regulatory requirements and principles for the ethical conduct of research, a Data Safety Monitoring Board (DSMB) will be formed to oversee the safety of study participants. Additionally, every PCRC study is required to have at least yearly PCRC Scientific Committee and site-level IRB review; each study site investigator will report events to their respective IRB on an annual basis or more often according to local IRB requirements.

Because the study population has, per the eligibility criteria, a limited expected prognosis of less than one year, hospitalization and death are expected to be common events over the course of the study due to natural progression of disease. Any event due to presence or progression of illness that a patient had on study enrollment will not be considered an adverse event (AE), including changes in symptoms, hospitalizations, emergency department presentations, and death more likely related to disease progression than not related to disease progression. Only events more likely not related to known underlying illness will be considered an AE. If such an event is also related to the research and is unanticipated, regardless of its level of severity, this would require expedited (prompt) reporting to the local IRB in keeping with its reporting requirements for a suspected unanticipated problem involving risks to subjects or others (suspected UPIRTSO).

AEs are classified as to whether or not they are serious (SAE), namely life threatening (resulting in hospitalization, emergency department presentation or death), related to a new congenital abnormality, leading to permanent disability, or judged a SAE by the site PI. AEs will be graded according to seriousness, and then designated as more likely expected or unexpected (yes/no), and more likely related or unrelated to the research (yes/no). Other characteristics of the AE to be recorded include date identified, diagnosis, outcome and date resolved.
SAEs will be classified as to whether or not they are a suspected unexpected serious adverse reaction (SUSAR). SUSARs are defined as events that are a suspected adverse reaction AND serious AND unexpected. This approach focuses the DSMB and IRB’s attention on potentially intervention-related events rather than on a large number of anticipated events that are part of normal disease progression and unrelated to the intervention. If a SUSAR, then expedited reporting and processes must be followed, as outlined below. If not a SUSAR, standard reporting for AEs is followed (for all AEs and SAEs), unless, as described above, the event meets the definition of a suspected UPIRTSO. An event can be a SAE, but not a SUSAR (e.g. person hospitalized for hip fracture and not attributable to underlying known illnesses, but not suspected to be related to the study intervention).

To ensure that hospitalizations and deaths are indeed unrelated to the research, hospitalizations and deaths will be closely monitored by the study’s Event Classification Committee (ECC) and DSMB. The ECC will review a pre-specified proportion of all hospitalizations and deaths. The ECC will determine if the hospitalization/death was an expected event, SAE or SUSAR. Results will be reported to the DSMB, and DSMB action will be according to the DSMB charter.

Cumulative aggregated AE data will be presented to the DSMB, along with tabulated outcomes data. This includes AEs, SAEs and SUSARs, plus survival, health resource utilization, and patient reported outcomes. The DSMB will meet at least every 6-12 months, according to the DSMB charter. The DSMB makes all decisions regarding continuing or discontinuing the trial in light of SUSARs, AEs and patient outcomes; DSMB recommendations are presented to the Study Co-PIs according to the DSMB charter.

The Study Co-PIs are also responsible for contacting the NIH grant program director in the event that any action resulting in temporary or permanent suspension of the trial occurs. (Because this trial does not involve any investigational medication, the action would be limited to an IRB- or investigator- initiated suspension or discontinuation of the study.)
8 References