

1                   **Default Options in Advance Directives for Seriously Ill**  
2                   **Patients: A Randomized Clinical Trial**

3  
4                   **Study Protocol and Statistical Analysis Plan**

5  
6                   A prospective randomized controlled trial to examine whether structuring advance directives to  
7                   request comfort-oriented goals of care by default improves patients' quality of life and reduces  
8                   resource utilization without reducing the number of days that patients are alive and living  
9                   outside of an acute-care hospital.

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154 **I. Original Protocol**  
155

156 **1. Abstract**

157 Although most seriously ill Americans wish to avoid burdensome therapies near life’s end,  
158 aggressive care is provided unless or until patients or their family members actively request  
159 that it is stopped. Advance directives (ADs) hold great promise for combating this societal  
160 default of aggressive end-of-life care, but to date this promise has been largely unrealized. This  
161 study will test the premise that ADs can better align the end-of-life care patients receive with  
162 the care they want if the ADs are restructured such that comfort-oriented care is provided as  
163 the default, rather than forcing patients to make emotionally and existentially challenging  
164 choices to receive it. In this study, we will determine whether this simple and readily scalable  
165 intervention can improve patients’ quality of life and reduce resource utilization without  
166 reducing the number of days that patients are alive and living outside of an acute-care hospital.

167 **2. Background and Significance**

168 Most Americans wish to die at home and to avoid aggressive care and life support when  
169 terminally ill. Yet the opposite commonly happens: one in five Americans dies in or shortly  
170 following a stay in an intensive care unit (ICU), roughly half of U.S. deaths occur in a hospital  
171 one third of elderly patients undergo an inpatient surgical procedure during their last year of  
172 life, one half of elderly Americans visit emergency departments in the last month of life, and  
173 more than one quarter of Medicare dollars are spent on patients in their final year. Perhaps  
174 even more concerning are recent observations that aggressive treatment of patients with  
175 serious illnesses is associated with reduced quality and perhaps quantity of life near its end.  
176 When such care culminates in ICU-based deaths, it also produces long-lasting pathological  
177 bereavement among family members contravening most patients’ strong desires not to burden  
178 their loved ones.

179  
180 Despite past failures, written advance directives (ADs) hold great promise. A recent study  
181 highlights a key reason for the discrepancy between the care we want and the care we receive  
182 near life’s end: critical healthcare decisions must be made for 43% of older Americans near the  
183 times of their deaths, but 70% of these patients cannot participate in making these decisions.  
184 The cumulative result – that 30% of older Americans cannot choose their care when such  
185 choices are needed – highlights the potential benefits of improving the quality of advance care  
186 planning, including written advance directives (ADs).

187  
188 ADs include living wills, in which patients can choose to receive or avoid life-sustaining  
189 therapies if they lose capacity to make such decisions, and designation of a durable power of  
190 attorney for healthcare to serve as the patient’s decision-maker in similar circumstances. Many

191 experts have bemoaned the shortcomings of ADs, particularly for the living will component .  
192 Such concerns have spawned a broader focus on advance care planning that seeks to prepare  
193 patients and family members for difficult decisions. Sound in principle, this approach is difficult  
194 in process. For the right patient, surrounded by the right family, and cared for by the right  
195 clinicians, such coordinated communication may prove optimal. But this approach may be  
196 difficult to implement across diverse populations with differential access to longitudinal care.

197 By contrast, fixing the problems with ADs may yield more scalable ways to improve end-of-life  
198 care for all Americans. Recent evidence provides substantial motivation to try. Observational  
199 studies in the United States show that elderly patients who complete ADs less commonly die in  
200 a hospital, more often receive care consistent with their preferences, and receive less costly  
201 care.

202 Despite these recent studies showing the promise of ADs, none provide sufficient evidence that  
203 completing ADs, or certain types of ADs, will cause changes in clinical, economic, or patient-  
204 centered outcomes. Studies noting improved patient-centered and economic outcomes among  
205 patients completing ADs were all observational in nature, preventing conclusions about  
206 whether AD completion caused these benefits or was a marker for people likely to attain them  
207 anyway. Thus, given federal policies promoting AD completion, and evidence that completion  
208 rates are increasing in the U.S., an RCT is desperately needed to determine how best to design  
209 ADs to improve patient outcomes without increasing resource utilization.

### 210 **3. Objectives**

#### 211 **3.1 Overall objectives**

212 This study will test the premise that ADs can better align the end-of-life care patients receive  
213 with the care they want if the ADs are restructured such that comfort-oriented care is provided  
214 as the default, rather than forcing patients to make emotionally and existentially challenging  
215 choices to receive it.

#### 216 **3.2 Primary outcome variable(s)**

217 The primary outcome is “Hospital-Free Days” (HFDs), a measure that PI Halpern has been  
218 developing in collaboration with Dr. Jeffrey Silber at Penn’s Center for Outcomes Research. As  
219 the name describes, HFDs represent the number of days alive and not in an acute care facility.  
220 Although this is a simple concept and provides an outcome measure of obvious importance to  
221 patients, the use of HFDs as a primary outcome in an RCT is highly innovative. To bolster  
222 confidence in the results, we will evaluate two key variations on the theme. First, we will  
223 explore “Healthcare Facility-Free Days,” which represents the number of days alive where a  
224 patient is neither in an acute care facility, a chronic care facility, nor a nursing home. We will  
225 also evaluate HFDs within a defined period of follow-up – 6 months in this case. This is  
226 analogous to the established outcome of ventilator-free days used commonly in RCTs among

227 ICU patients.

228 **3.3 Secondary outcome variable(s)**

- 229 1. Hospital and ICU admissions: The numbers of admissions will be analyzed as count data.  
230 From the dates of hospital and ICU admissions, we will calculate the proportion of each  
231 patient's total survival time during study follow-up that was spent in the hospital or ICU.
- 232 2. Costs of care: We will combine all costs of inpatient and outpatient hospice, hospital  
233 stays, and life-sustaining procedures. The perspective will be that of all potential  
234 payers. Costs will be inflated to the date on which analyses are performed using the U.S.  
235 gross domestic product deflator.
- 236 3. Hospice utilization: We will analyze hospice utilization in 2 ways: (a) time from AD  
237 completion to hospice enrollment; and (b) duration of hospice utilization prior to death.
- 238 4. Choices to receive 4 potentially life-sustaining interventions, and the concordance of  
239 these choices with whether the interventions were actually received: The outcomes  
240 databases we will use contain codes for each of the 4 interventions, enabling us to  
241 determine which patients received each. Thus, we will be able to reliably evaluate the  
242 proportions of patients who received unwanted interventions. Because we cannot  
243 determine the denominator of patients with indications for these interventions, we will  
244 not evaluate the proportions of patients who went without desired services.
- 245 5. Choices regarding post-hospitalization care, and the concordance of these choices with  
246 the care actually received.
- 247 6. Decision regret and satisfaction: Decision regret will be measured using the 5-item  
248 decision regret scale that has previously been shown to have good internal consistency  
249 and strong inverse associations with decision satisfaction. Satisfaction will also be  
250 measured more specifically with the CANHELP instrument's global satisfaction with end-  
251 of-life care question.
- 252 7. Quality of life, using the McGill Quality of Life (MQOL) instrument. The MQOL is a well-  
253 validated and widely used scale designed specifically for patients with serious illnesses.  
254 The MQOL can be completed by family members on behalf of patients who have lost the  
255 capacity to complete it. Thus, we will have surrogates complete the MQOL for  
256 incapacitated patients to minimize missing data.
- 257 8. Surrogates' Perception of the quality of death and dying: We will assessed this outcome  
258 with surrogates of deceased patients using the quality of dying and death (QODD)  
259 instrument.
- 260 9. Bereavement outcomes: The risk of post-traumatic stress disorder in surrogates among  
261 deceased patients will be assessed using the Impact of Events Scale (IES). The IES is a  
262 valid and reliable scale that has been used frequently to assess PTSD risk among family  
263 members of critically ill patients. Finally, complicated grief will be assessed using

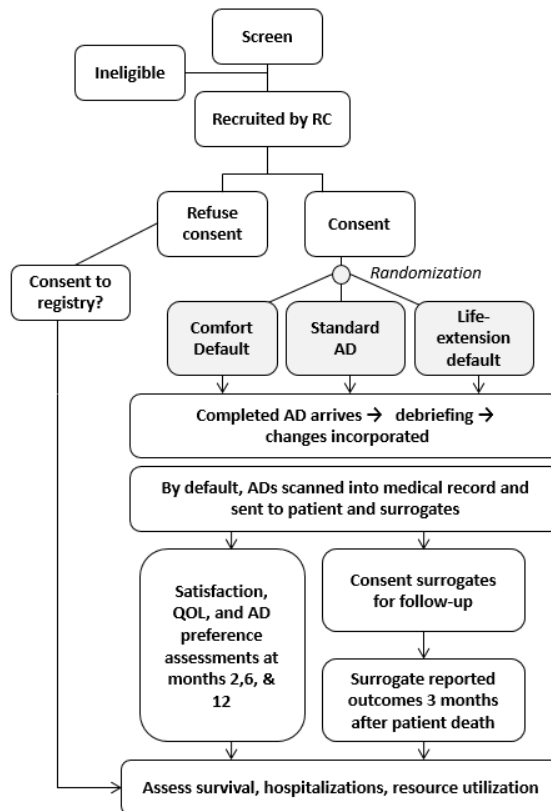


264 Prigerson’s Inventory of Complicated Grief to distinguish pathologic grieving from  
265 normal bereavement.  
266

#### 267 4. Study Design

##### 268 4.1 Schema

269 This is a prospective, randomized, controlled trial.



270

271

##### 272 4.2 Duration

273 The study period is two years. Subjects will be accrued over a period of 18 months starting in  
274 January 2014. The total time it will take for the research coordinator to explain the study,  
275 obtain consent and for a subject to complete the advance directive will, conservatively, take no  
276 more than two hours. The debriefing discussion and follow up interviews will take  
277 approximately 15 – 25 minutes each. The total time spent on research activities for patients  
278 should be no more than 4 hours.

279

## 280 **5. Subject recruitment**

281  
282 We will recruit 270 patients with severe respiratory, oncological, neuromuscular, or  
283 cardiovascular diseases and limited life expectancy from the Perelman Center for Advance Care  
284 Medicine, Penn Presbyterian Medical Center, Pennsylvania Hospital, and the University of  
285 Pittsburgh Medical Center. Each week the research coordinators will screen the electronic  
286 medical records of patients scheduled for routine visits to determine their study eligibility using  
287 the eligibility criteria outlined above.

288 Once eligible patients have been identified, research coordinators will email eligible patients'  
289 providers to 1) alert them to their patients' eligibility for participation 2) inform them their  
290 patients will be recruited for enrollment 3) provide them an opportunity to decline or defer any  
291 given patient's enrollment by responding to the email. Research coordinators will approach  
292 potential study participants while they are in the waiting areas, chemotherapy infusion areas,  
293 or in exam rooms waiting to see their doctor on the day of their visit.

### 294 **5.1 Accrual**

295 During our pilot study we were able to recruit approximately six patients per month with one  
296 full-time research coordinator. We anticipate that with the equivalent of 3.5 full-time research  
297 coordinators and an additional site (University of Pittsburgh), we will be able to recruit  
298 approximately 18 patients per month.

### 299 **5.2 Key inclusion criteria**

300 The eligibility criteria, all of which must be met, are:

- 301 1. Age 18 or older
- 302 2. Speaks and reads fluent English
- 303 3. Has seen current physician at least once prior to current visit
- 304 4. Resident of Pennsylvania or New Jersey
- 305 5. One or more of the following diagnoses:
  - 306 • Amyotrophic lateral sclerosis
  - 307 • Stage IIIB or IV non-small cell lung cancer, pancreatic cancer, or cholangiocarcinoma
  - 308 • Stage IV colorectal, esophageal, gastric (including GIST), pancreatic, prostate, or
  - 309 urothelial cancer; paraganglioma, or pheochromocytoma
  - 310 • Stage C or D hepatocellular carcinoma
  - 311 • Stage IV renal cell carcinoma
  - 312 • Stage IV or V chronic kidney disease
  - 313 • Mesothelioma or any malignancy metastatic to the pleura
  - 314 • Other incurable interstitial lung diseases with at least severe restriction on most recent
  - 315 pulmonary function tests or eligible for long-term oxygen therapy
  - 316

- 317 • Chronic obstructive pulmonary disease with at least severe airflow obstruction on most  
318 recent spirometry or eligible for long-term oxygen therapy
- 319 • Congestive heart failure with NYHA Class IV status or Class III plus 1 heart failure related  
320 hospitalization in the past 12 months or ACC stage D or C classification with 1 heart  
321 failure related hospitalization in the past 12 months
- 322 • Stage IV breast cancer except patients whose only metastases are to the bones or who  
323 are receiving endocrine therapy without receiving concomitant traditional  
324 chemotherapy

### 325 **5.3 Key exclusion criteria**

326 Patients will be excluded if they are currently listed for or being considered for solid organ  
327 transplant and if they have a previously signed advance directive or living will. Cognitively  
328 impaired patients will be excluded from the study to avoid the necessity of proxy consent.

### 329 **5.4 Subject Remuneration**

330 Patients will be compensated with \$20 at the day of enrollment in cash. In order to enhance  
331 study retention and participation in follow-up assessments, \$20 will also be paid to subjects at  
332 the completion of the two, six, and twelve month follow-ups. Surrogates will also be  
333 compensated \$20 after they consent to participate.

## 334 **6. Randomization**

335

### 336 **6.1 Groups**

337

338 Subjects enrolled in this RCT will be randomized into three groups. Depending on which group  
339 they've been assigned, subjects will be given one of three AD forms. The three AD forms have  
340 been created with different default treatment options. Form 1 (life-extension default) will state  
341 that 4 specific life-extending interventions (cardiopulmonary resuscitation, mechanical  
342 ventilation, hemodialysis, and feeding tube insertion) will be provided unless patients  
343 specifically opt-out from such selections. Form 2 (comfort default) will state that the 4 specific  
344 life-extending interventions will not routinely be provided unless patients elect to receive such  
345 measures. Finally, Form 3 (standard advance directive) will use the standard approach of  
346 requiring patients to actively choose whether or not they wish to receive each intervention, as  
347 they would if completing an AD outside of a research setting. In this case, if they do not make a  
348 selection, decision making would default to their surrogates as in usual practice.

349  
350 Because patients may focus on an overall plan of care rather than the receipt of specific  
351 interventions, all AD forms will also include a general question regarding treatment priorities.  
352 The response to this question, is modeled on one used in a Study to Understand Prognoses and

353 Preferences for Outcomes and Risks of Treatments (SUPPORT) study. The question  
354 acknowledges that while, in general, most people wish to both live as long as possible and avoid  
355 pain and suffering, in some situations, choosing between these two goals may be necessary. It  
356 then asks patients, if they are in a situation where such a choice is needed, whether they prefer  
357 a plan of care that focuses on extending life as much as possible even if it means having more  
358 pain and suffering, or a plan of care that focuses on relieving pain and suffering even if that  
359 means not living as long. The default framing of this general question will be in accord with that  
360 used for the specific interventions in each AD form, and all patients will be able to select a “no”  
361 option in response to this question.

362  
363 Finally, we will include a specific question about the care patients wish to receive upon  
364 discharge from the hospital, defaulting to hospice-based care (in the comfort-default group),  
365 long-term care (in the life-extension-default group), or no option pre-selected. In the standard  
366 AD group, although no options will be pre-selected, we will randomly assign whether the  
367 comfort-oriented option or the life-extending-oriented option is presented first so as to  
368 mitigate ordering effects. In all cases, the option of not deciding will be presented last.

## 369 **6.2 Assignment**

370  
371 Eligible patients will be approached about participation by the research coordinators in the  
372 outpatient clinics at the Perelman Center for Advanced Medicine, Pennsylvania Hospital, and  
373 Presbyterian Hospital. Consenting subjects will be randomized with a 33.3% probability to each  
374 trial arm (life extension default, comfort default, standard AD) using electronic procedures  
375 monitored by the Data Management Unit within the Biostatistics Analysis Center. We will  
376 stratify the randomization by recruiter/research coordinator, and will use variable block sizes of  
377 3 and 6 patients to promote balance of follow-up duration among the 3 trial arms.

378  
379 Each research coordinator will go to his or her clinics each day with a sealed envelope in which  
380 there is a pre-determined sequence of the 3 trial packets. The research coordinator will become  
381 unblinded to the patient’s allocation at the time of consent, but with variable block sizes, can  
382 never predict with certainty what the next packet will be.

383

## 384 **7. Study Procedures**

385

### 386 **7.1 Screening for Eligibility**

387

388 The research coordinators will screen electronic medical records of patients visiting pulmonary,  
389 renal, heart failure, movement disorder, and oncology clinics at the Perelman Center for

390 Advance Care Medicine, Penn Presbyterian Medical Center, Pennsylvania Hospital and the  
391 University of Pittsburgh Medical Center for eligibility. Patient's eligibility status will be entered  
392 into the eligibility database. We will record ICD9 and ICD 10 codes, staging information,  
393 relevant provider name, clinic location, and upcoming appointments for eligible patients.  
394

## 395 **7.2 Recruitment**

396  
397 Eligible patients will be approached by a research coordinator in the clinics who will seek  
398 patients' consent to participate in a study comparing different types of ADs. Of note, while  
399 some providers may be more proactive than others in engaging their patients in conversations  
400 about advance care planning, it is generally not standard-of-care that patients are approached  
401 about completing ADs. The research coordinator will specify that the ADs in this study are  
402 intended to be real ADs and that they will be included in patients' outpatient medical records,  
403 but that, as with all ADs, patients retain the right to change their selections at later dates. The  
404 research coordinator will also specify that, like all real ADs, they are most useful if copies are  
405 shared with their loved ones and physicians.  
406

## 407 **7.3 Informed Consent**

408  
409 Following discussion of the study, research coordinators will obtain written consent from  
410 patients. The consent forms will contain HIPAA statements of authorization of release of  
411 medical records, thus facilitating our collection of data from medical and billing records during  
412 the study. The consent includes clear explanations that different types of ADs will be assigned  
413 by chance, but that patients in all groups may select or decline any intervention or treatment  
414 goal, and may revise their choices at any time. The research coordinators will explain who will  
415 be enrolled, how many patients are being targeted for enrollment, the specific components of  
416 patient follow-up, patients' rights to withdraw from the study at any time and for any reason,  
417 and what the outcomes of interest are (e.g., utilization of healthcare services, AD selections).  
418

419 Patients who do not wish to complete an AD and decline consent will be asked to instead sign a  
420 limited consent form that would provide authorization to assess their long term health  
421 outcomes from electronic health records, but would not entail any further direct patient  
422 contact. The goal of this research would be to compare the outcomes of patients who have an  
423 advance directive against those who do not. Consenting patients would agree to participate in a  
424 registry by providing their social security number for purposes of merging with state  
425 maintained datasets described in detail below. Patients who agree to participate in the registry  
426 would also provide their age, race, ethnicity, and gender.

427

#### 428 **7.4 Enrollment**

429

430 After patient consent is obtained, the research coordinator will ask subjects to complete the  
431 demographics survey and walk subjects through the process of filling out the AD. Along with  
432 their AD forms, consenting subjects will be given a copy of their consent form, an informational  
433 brochure about advance care planning, contact information for research study staff,  
434 instructions for mailing back their completed AD forms, and a stamped and addressed  
435 envelope. To enhance retention, patients will also be given \$20 at the point of consent.

436

437 Subject IDs will be assigned at the point of consent. Subject ID numbers, demographic  
438 information and group assignments will be entered into the analytic database. Subject contact  
439 information, including social security number, will be entered into a subject tracking database.

440

441 If completed ADs are not returned within 10 days, staff will call patients weekly to remind them  
442 to return their ADs, to schedule special clinic visits for AD completion if patients desire, and to  
443 answer any questions. If research staff members are unable to reach patients over the phone  
444 after three attempts, a letter will be sent to patients to remind them to return their ADs and  
445 encourage them to contact research staff if they have any questions or difficulties. If we are still  
446 unable to reach patients, they will be approached by the research coordinator in their next  
447 clinic visit.

448

#### 449 **7.5 Subject Debriefing**

450

451 After patients complete their assigned AD, there will be a structured debriefing session  
452 conducted over the phone by a research team member in which a standardized explanation of  
453 all three ADs will be given. This debriefing will be held to alert patients to exactly how the three  
454 ADs used in the study differ. As in the pilot study, patients will not be alerted to the different  
455 default framings up front because patients in clinical settings (and indeed in this study) are only  
456 asked to complete a single AD. Explaining non-relevant ADs prior to completion of the relevant  
457 one could influence decisions in ways that would not reflect actual clinical settings, thereby  
458 biasing the results. However, because this is a research study and AD assignment is at random,  
459 it is appropriate to debrief patients afterwards to grant them such broader information. Once  
460 patients are fully informed about the variations in the ADs used in the study, they will be asked  
461 if they wish to change any of their AD selections prior to finalizing the documents as a part of  
462 the medical record. Patient ADs will not be considered “complete” until the debriefing session

463 has taken place. After the debriefing call, patients' AD selections will be entered into the  
464 analytic database.

465  
466 During the debriefing call, we will tell subjects that we will scan their AD forms into their  
467 medical records for them, unless they do not desire this (it is optional, not a requirement of the  
468 study). Similarly, we will also inform subjects that a copy of their completed AD will be sent  
469 back to them, and that, if they wish, a copy will be sent to their appointed healthcare  
470 agent/surrogate. Completed ADs will be sent to patients and surrogates along with letters  
471 explaining that ADs can be changed at any time and they can contact the research team with  
472 questions.

473  
474 The research team will contact the appointed health care agent/surrogate identified in  
475 completed AD forms to seek the surrogate's consent to a) contact him or her in the event that  
476 we are unable to reach the patient for follow-up, and b) participate in an interview related to  
477 surrogate outcomes participate in follow-up and surrogate interviews. We will also ask  
478 surrogates to notify the research team if patients die during follow-up. The research team will  
479 also contact the appointed health care agent/surrogate identified in completed AD forms to  
480 seek the surrogate's consent to a) contact him or her in the event that we are unable to reach  
481 the patient for follow-up b) participate in an interview related to surrogate outcomes  
482 participate in follow-up and surrogate interviews. We will also ask surrogates to notify the  
483 research team if patients die during follow-up. This consent process will take place over the  
484 phone and, thus, we are requesting a waiver of documentation of informed consent.

485

## 486 **7.6 Subject Follow-up**

487

488 Two, six, and twelve months after AD completion, subjects will be contacted for participation in  
489 follow-up interviews. The follow-up interviews will take place over the phone with a research  
490 associate blinded to the subject's study arm. The research associates will attempt to contact  
491 patients up to three times over the phone. If the research associates are unable to reach the  
492 patients, they will inform the research coordinator. The research coordinator will contact the  
493 patients in person the next time they arrive in clinic to ensure that patients do not have any  
494 questions or concerns about their participation in the study and set-up a time for the follow-up  
495 call. If patients are unavailable to participate in follow-up calls because they are deceased or  
496 otherwise incapacitated, we will interview their surrogates.

497

498 In the event of a patient's death, a research associate will contact the patient's surrogate  
499 between 2-3 months after the death for a telephone interview. During the telephone interview  
500 the research associate will assess quality of death and dying and bereavement outcomes using

501 the Quality of Dying and Death (QODD) instrument, the Impact of Events Scale (IES), and  
502 Prigerson's Inventory of Complicated Grief.

503

## 504 **7.7 Assessment of Health Outcomes**

505

506 We will assess hospitalizations, ICU admissions, costs of inpatient care, and utilization of life-  
507 sustaining therapies by querying state-run databases that capture all admissions and inpatient  
508 procedures in Pennsylvania and New Jersey. The Pennsylvania Health Care Cost Containment  
509 Council (PHC4) is an independent state agency that maintains a database of inpatient hospital  
510 discharge and outpatient procedure records from all hospitals and ambulatory surgery centers  
511 in Pennsylvania. These data include specific treatment information including costs. As roughly  
512 one-third of Penn's outpatient population resides in New Jersey, we will obtain comparable  
513 data from the New Jersey Discharge Data Collection System (NJDDCS) managed by the New  
514 Jersey Department of Health and Senior Services within their Department of Health Care  
515 Quality and Assessment (HCQA). We will establish data use agreements with both of these  
516 entities and be subject to IRB approval by HCQA. Linkages with both PHC4 and NJDDCS will be  
517 performed by the respective database administrators after we provide lists of included social  
518 security numbers and subject IDs. PHC4 and NJDHSS will send our team a report in which  
519 patients are identified by subject ID only. Identical processes have been used seamlessly and  
520 with high fidelity by many Penn investigators.

521

522 We will collect data on hospice utilization and costs via data use agreements with Penn  
523 Wissahickon Hospice and Family Hospice and Palliative Care. These organizations provide  
524 hospice services for 80% of Penn and Pitt patients, respectively.

525

## 526 **8. Data Management**

### 527 **8.1 Data Confidentiality**

528 Only authorized project personnel will have access to the data. All study data will be stored behind  
529 firewalls on Center for Clinical Epidemiology and Biostatistics (CCEB) servers; none will be stored on  
530 stand-alone PCs or laptops. All study personnel who work with these data will have undergone required  
531 human subjects training. To ensure that participant confidentiality is preserved, individual identifiers  
532 (such as social security number) will only be used to link patient records (e.g., linking subject database to  
533 PHC4 data). Once linkages between databases have been achieved, all linkage-identifiers will be  
534 dropped from all datasets. Throughout the study duration, we will maintain one master list that will link  
535 study identification numbers to patient identifiers. This list will be maintained by the principal  
536 investigator in a locked file drawer in his locked private office to ensure file security. This file will be  
537 made available to other research staff on a need-to-know basis only, and, in that case, only temporarily.  
538 The study ID will be used exclusively in all analytical files.



539 All datasets and computer files with study ID numbers will be further secured as follows. The University  
540 of Pennsylvania (Penn) Data Management Unit (DMU) is an arm of the broader Biostatistics and  
541 Epidemiology Consulting Center (BECC), all of which is housed within the CCEB. The DMU will be the hub  
542 for the database infrastructure that will support the project. The DMU provides a secure computing  
543 environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and  
544 financial information. We will implement multiple, redundant protective measures to guarantee the  
545 privacy and security of the participant data. All data for this project will be stored on the  
546 secure/firewalled servers of the CCEB in data files that will be protected by multiple password layers.  
547 These data servers are maintained in a guarded facility behind several locked doors, with very limited  
548 physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of  
549 communication encryption. Electronic access rights are carefully controlled by Penn system managers.  
550 We will use highly secure methods of data encryption for all transactions involving participants' financial  
551 information using a level of security comparable to what is used in commercial financial transactions.  
552 This multi-layer system of data security, identical to the system protecting the University of  
553 Pennsylvania Health System's medical records, greatly minimizes privacy risks.

## 554 **8.2 Subject Confidentiality**

555 Steps will be taken to ensure that all information will be kept confidential and secure. Unique  
556 patient identifiers numbers will be assigned to each subject locally and kept in a secure  
557 encrypted file. Records with patient social security numbers will be maintained, used, and  
558 destroyed in a way that is consistent with Penn policy. All paper records will be kept in locked  
559 files; all computers will be password protected and kept in locked rooms; all databases will be  
560 password protected and maintained on encrypted hard-drives behind the CCEB firewall. All  
561 study data will be stored behind firewalls on Center for Clinical Epidemiology and Biostatistics  
562 (CCEB) servers; none will be stored on stand-alone PCs or laptops. All data will be destroyed  
563 after 7 years.

564

## 565 **8.3 Subject Privacy**

566 Individual-level data for participants will be kept confidential and will only be stored on highly  
567 secure servers available for patient-level data. Only authorized project personnel will have  
568 access to the data and the data will be stored on servers only and not stand-alone PCs or  
569 laptops. All study personnel who work with subject identifiers and contact information will have  
570 undergone all required human subjects training. They will work with the data in password  
571 protected files and once enrollment and follow up are complete, all identifying information will  
572 be removed. Personally identifiable information will NOT be included in the analytic database.

573

574 Potential subjects will be approached, in clinics, by highly trained research staff members who  
575 understand the importance of subject privacy. In most cases, the initial encounter with patients

576 will take place in private exam rooms or infusion suites. Potential subjects may be approached  
577 in waiting areas, but it will be done in a way that is sensitive to maintaining privacy.

578  
579 Follow-up phone calls will be conducted by trained research staff who will be calling, primarily,  
580 from their offices in Blockley Hall. Efforts will be made to ensure that phone calls will not be  
581 overheard by anyone who is not directly involved with the research. In the event that research  
582 staff member needs to leave a voicemail message for a subject, they will do so in a way that  
583 maintains subject privacy.

## 584 **9. Data and Safety Monitoring**

### 585 **9.1 Monitoring Plan**

586  
587 The data and safety monitoring plan will have 3 parts. First, the BECC will implement methods  
588 of validating entered data, as they have done for numerous trials before, thereby ensuring the  
589 quality of our data. Second, the PI will be directly responsible for identifying and reporting all  
590 serious adverse events, protocol deviations/violations, and unanticipated events to the IRBs  
591 and funding agency promptly, as appropriate. He will also report all adverse events, accrual  
592 rates, retention rates, mortality/survival data and all other logistical issues to the DSMB at least  
593 biannually (and more frequently as requested or needed). Third, we have convened a DSMB  
594 that will be responsible for monitoring the trial and making decisions about the termination of  
595 individual study arms or the study itself.

596  
597 The DSMB will consist of individuals with considerable expertise in human subjects research,  
598 vulnerable populations, bioethics, clinical trials, decision making, palliative care, and  
599 biostatistics. The PI (Dr. Halpern), the project manager (Elizabeth Cooney), and the lead  
600 statistician (Dr. Troxel), will participate in all DSMB meetings as non-voting members. The PI,  
601 assisted by the project manager, will be responsible for maintaining communication between  
602 the DSMB and the individual project staff.

603  
604 The DSMB will perform several duties. First, they will review and approve the research protocol  
605 and plans for data and safety monitoring. Second, they will evaluate the progress of the trial.  
606 This will include assessment of data quality, participant recruitment, accrual and retention,  
607 participant risk versus benefit, and study outcomes. This assessment will be performed at  
608 meetings every 6 months during the study and more frequently if needed. They will be paying  
609 particularly close attention to patient survival as well as selections made on advance directive  
610 forms. Third, they will make recommendations to ensure that all of the issues above are  
611 appropriately addressed. Dr. Halpern, as the study PI, will be responsible for responding to all  
612 recommendations of the DSMB and submitting DSMB reports to the Penn and Pitt IRBs.

613

## 614 **9.2 Data Safety Monitoring Board Members**

615

616 The DSMB has been constituted and includes the following members:

617

618 1. David Wendler, PhD: expertise in research with vulnerable populations and research ethics,  
619 including the role of debriefing in RCTs.

620 2. Vicki Jackson, MD, MPH: expertise in palliative care for dying patients, and physician-patient-  
621 family communication regarding end-of-life decisions.

622 3. Manisha Desai, PhD: expertise in statistical methods for the analysis of clinical trials,  
623 including the implementation of stopping rules.

624

625 The DSMB will also be responsible for reviewing the provided data at the 6 month and 1 year  
626 interim analyses, determining the scientific validity and safety to determine whether the study  
627 should be continued, and will advise the PI regarding whether to bring the project to a close.

628 The project manager, Elizabeth Cooney, and staff analyst, Dr. Nicole Gabler, will assist Drs.  
629 Halpern and Troxel in providing the DSMB with any additional information on request.

630

## 631 **10. Human Subjects Protection**

### 632 **10.1 Risk / Benefit Assessment**

633 This study presents no more than minimal risk. Many precautions will be taken to protect  
634 subjects against the most likely risk which is breach of confidentiality. In addition, the ADs are  
635 not legally binding and therefore are unlikely to erect barriers to patients receiving desired  
636 care. Instead, the ADs may merely help them avoid unwanted treatments. As a result, the  
637 potential benefits to individual subjects in terms of learning about ADs and to society from  
638 learning about a scalable intervention to improve the uptake, patient-centeredness, and  
639 effectiveness of advance directives far exceed the potential risk.

640

641 The potential risks to human subjects in this research include (1) risks of breach of  
642 confidentiality of personal health information (PHI), (2) risks of emotional distress brought on  
643 by being asked to contemplate end-of-life care, and (3) risks that the interventions could have  
644 untoward impacts on patients or their family members. Potential untoward impacts include  
645 unfavorable changes in quality of life, duration of life, satisfaction with end-of-life care  
646 planning, surrogate perceptions of the quality of dying and death, surrogate bereavement and  
647 psychiatric disturbance following deaths of loved ones, or altering (increasing or decreasing)  
648 utilization of interventions at the end of life in ways that patients would not prefer. Of note, we  
649 anticipate favorable – or at worst neutral – impacts on each of these outcomes, but are

650 designing our study to detect and respond quickly to unforeseen negative impacts in any of  
651 these domains.

652

653 Participants in this study may benefit directly from the opportunities to discuss and clarify their  
654 end-of-life care preferences with experienced personnel who can facilitate inclusion of these  
655 preferences into their future clinical care. Participants also may benefit from the knowledge  
656 that their surrogates have clear direction on their wishes and thus, may experience fewer  
657 burdens with difficult decision-making, perhaps alleviating subsequent stress or depression.  
658 However, participants will be instructed that this is research, and like all research, it is being  
659 conducted with the primary goal of producing generalizable knowledge. Thus, the primary  
660 benefits to be gained are those related to the knowledge to be gained.

661

662 The knowledge to be gained in this study may be of considerable importance. Given the  
663 widespread dissatisfaction with the quality of end-of-life care in the U.S., this randomized trial a  
664 readily scalable intervention to improve the uptake, patient-centeredness, and effectiveness of  
665 advance directives, which stems from a novel and innovative conceptual framework, holds  
666 great promise for improving public health. The simple and inexpensive methods to be tested  
667 may go a long way towards narrowing the gap between the care patients prefer near the end of  
668 life and the care they actually receive.

669

## 670 **10.2 Protective Measures**

671 The first safeguard for protection of human subjects includes an experienced and well-trained  
672 study team. Dr. Scott Halpern (PI) is the Principal investigator. He has substantial experience  
673 conducting RCTs of behavioral economic interventions to modify health-related behaviors, in  
674 the ethics of applying behavioral economics to health decisions, and in the design, ethics, and  
675 recruitment barriers of RCTs. As Principal Investigator for the proposed trial, Dr. Halpern will be  
676 primarily responsible for the completion of all aspects of this RCT including study design,  
677 underlying data infrastructure, compliance with IRB requests and requirements, participant  
678 recruitment, data collection and management, data analysis, adherence to all policies and  
679 procedures for clinical research.

680 Collaborating with Dr. Halpern as co-investigators and overseeing recruitment at the University  
681 of Pittsburgh are Drs. Cindy Bryce and Doug White. Dr. Bryce is a health services researcher  
682 who has spent considerable time investigating the use of decision science to improve medical  
683 decision-making in the context of critical illness. In addition to overseeing the implementation  
684 of this study at Pitt, she brings her expertise as an investigator in preference-based assessment  
685 of quality-of-life, cost effectiveness analysis, and behavioral decision theory for understanding  
686 patient and surrogate decision making. Dr. White directs the University of Pittsburgh Program

687 on Ethics and Decision-Making in Critical Illness, which encompasses both empirical research  
688 on, and normative ethical analysis of decision-making for, patients with life-threatening illness.  
689 He will work with Dr. Bryce in coordinating the logistics and oversight of the study at Pitt and  
690 will assist Dr. Halpern's team at Penn in interpreting results and preparing manuscripts related  
691 to his area of particular expertise – surrogate decision-making.

692 All study team members have completed training in HIPAA regulations and human subjects  
693 research.

694 The debriefing process is an important element of human subjects protection. It will ensure  
695 that patients (1) understand their selections on their AD forms; (2) do not simply go with the  
696 default options because they failed to recognize that a choice was to be made or that a default  
697 was being used; (3) have multiple opportunities to withdraw their participation or data; and (4)  
698 are actively engaged in the research and comfortable with the research process.

699 Additional layers of protection for human subjects include the robust informed consent process  
700 (section 7.3), exceptional data security (sections 9.1, 9.2 & 9.3), and the empowered Data  
701 Safety and Monitoring Board (sections 10.1 & 10.2), all described in detail in this protocol.

702 **This original protocol was finalized on January 9, 2014.**

703

## 704 II. Final Protocol

705

### 706 **1. Abstract**

707 Although most seriously ill Americans wish to avoid burdensome therapies near life's end,  
708 aggressive care is provided unless or until patients or their family members actively request  
709 that it is stopped. Advance directives (ADs) hold great promise for combating this societal  
710 default of aggressive end-of-life care, but to date this promise has been largely unrealized. This  
711 study will test the premise that ADs can better align the end-of-life care patients receive with  
712 the care they want if the ADs are restructured such that comfort-oriented care is provided as  
713 the default, rather than forcing patients to make emotionally and existentially challenging  
714 choices to receive it. In this study, we will determine whether this simple and readily scalable  
715 intervention can improve patients' quality of life and reduce resource utilization without  
716 reducing the number of days that patients are alive and living outside of an acute-care hospital.

### 717 **2. Background and Significance**

718

719 Most Americans wish to die at home and to avoid aggressive care and life support when  
720 terminally ill. Yet the opposite commonly happens: one in five Americans dies in or shortly  
721 following a stay in an intensive care unit (ICU), roughly half of U.S. deaths occur in a hospital  
722 one third of elderly patients undergo an inpatient surgical procedure during their last year of  
723 life, one half of elderly Americans visit emergency departments in the last month of life, and  
724 more than one quarter of Medicare dollars are spent on patients in their final year. Perhaps  
725 even more concerning are recent observations that aggressive treatment of patients with  
726 serious illnesses is associated with reduced quality and perhaps quantity of life near its end.  
727 When such care culminates in ICU-based deaths, it also produces long-lasting pathological  
728 bereavement among family members contravening most patients' strong desires not to burden  
729 their loved ones.

730  
731 Despite past failures, written advance directives (ADs) hold great promise. A recent study  
732 highlights a key reason for the discrepancy between the care we want and the care we receive  
733 near life's end: critical healthcare decisions must be made for 43% of older Americans near the  
734 times of their deaths, but 70% of these patients cannot participate in making these decisions.  
735 The cumulative result – that 30% of older Americans cannot choose their care when such  
736 choices are needed – highlights the potential benefits of improving the quality of advance care  
737 planning, including written advance directives (ADs).

738  
739 ADs include living wills, in which patients can choose to receive or avoid life-sustaining  
740 therapies if they lose capacity to make such decisions, and designation of a durable power of  
741 attorney for healthcare to serve as the patient's decision-maker in similar circumstances. Many  
742 experts have bemoaned the shortcomings of ADs, particularly for the living will component.  
743 Such concerns have spawned a broader focus on advance care planning that seeks to prepare  
744 patients and family members for difficult decisions. Sound in principle, this approach is difficult  
745 in process. For the right patient, surrounded by the right family, and cared for by the right  
746 clinicians, such coordinated communication may prove optimal. But this approach may be  
747 difficult to implement across diverse populations with differential access to longitudinal care.

748 By contrast, fixing the problems with ADs may yield more scalable ways to improve end-of-life  
749 care for all Americans. Recent evidence provides substantial motivation to try. Observational  
750 studies in the United States show that elderly patients who complete ADs less commonly die in  
751 a hospital, more often receive care consistent with their preferences, and receive less costly  
752 care.

753 Despite these recent studies showing the promise of ADs, none provide sufficient evidence that  
754 completing ADs, or certain types of ADs, will cause changes in clinical, economic, or patient-  
755 centered outcomes. Studies noting improved patient-centered and economic outcomes among

756 patients completing ADs were all observational in nature, preventing conclusions about  
757 whether AD completion caused these benefits or was a marker for people likely to attain them  
758 anyway. Thus, given federal policies promoting AD completion, and evidence that completion  
759 rates are increasing in the U.S., an RCT is desperately needed to determine how best to design  
760 ADs to improve patient outcomes without increasing resource utilization.<sup>20,34</sup>

### 761 **3. Objectives**

#### 762 **3.1 Overall objectives**

763 This study will test the premise that ADs can better align the end-of-life care patients receive  
764 with the care they want if the ADs are restructured such that comfort-oriented care is provided  
765 as the default, rather than forcing patients to make emotionally and existentially challenging  
766 choices to receive it.

#### 767 **3.2 Primary outcome variable(s)**

768 The primary outcome is “Hospital-Free Days” (HFDs), a measure that PI Halpern has been  
769 developing in collaboration with Dr. Jeffrey Silber at Penn’s Center for Outcomes Research. As  
770 the name describes, HFDs represent the number of days alive and not in an acute care facility.  
771 Although this is a simple concept and provides an outcome measure of obvious importance to  
772 patients, the use of HFDs as a primary outcome in an RCT is highly innovative. To bolster  
773 confidence in the results, we will evaluate two key variations on the theme. First, we will  
774 explore “Healthcare Facility-Free Days,” which represents the number of days alive where a  
775 patient is neither in an acute care facility, a chronic care facility, nor a nursing home. We will  
776 also evaluate HFDs within a defined period of follow-up – 6 months in this case. This is  
777 analogous to the established outcome of ventilator-free days used commonly in RCTs among  
778 ICU patients.<sup>35</sup>

#### 779 **3.3 Secondary outcome variable(s)**

- 780 1. Hospital and ICU admissions: The numbers of admissions will be analyzed as count data.  
781 From the dates of hospital and ICU admissions, we will calculate the proportion of each  
782 patient’s total survival time during study follow-up that was spent in the hospital or ICU.
- 783 2. Costs of care: We will combine all costs of inpatient and outpatient hospice, hospital  
784 stays, and life-sustaining procedures. The perspective will be that of all potential  
785 payers. Costs will be inflated to the date on which analyses are performed using the U.S.  
786 gross domestic product deflator.
- 787 3. Choices to receive 4 potentially life-sustaining interventions, and the concordance of  
788 these choices with whether the interventions were actually received: The outcomes  
789 databases we will use contain codes for each of the 4 interventions, enabling us to  
790 determine which patients received each. Thus, we will be able to reliably evaluate the  
791 proportions of patients who received unwanted interventions. Because we cannot

- 792 determine the denominator of patients with indications for these interventions, we will  
793 not evaluate the proportions of patients who went without desired services.
- 794 4. Choices regarding post-hospitalization care, and the concordance of these choices with  
795 the care actually received.
- 796 5. Decision conflict and satisfaction: The Decision Conflict Scale is a well-validated  
797 instrument used to assess patients' certainty in making healthcare decisions.  
798 Satisfaction will also be measured more specifically with the CANHELP instrument's  
799 global satisfaction with end-of-life care question.
- 800 6. Quality of life, using the McGill Quality of Life (MQOL) instrument. The MQOL is a well-  
801 validated and widely used scale designed specifically for patients with serious illnesses.  
802 The MQOL can be completed by family members on behalf of patients who have lost the  
803 capacity to complete it themselves. Thus, we will have surrogates complete the MQOL  
804 for incapacitated patients to minimize missing data.
- 805 7. Surrogates' Perception of the quality of death and dying: We will assess this outcome  
806 with surrogates of deceased patients using Prigerson's Quality of Death measures.
- 807 8. Bereavement outcomes: The risk of post-traumatic stress disorder in surrogates among  
808 deceased patients will be assessed using the Impact of Events Scale (IES). The IES is a  
809 valid and reliable scale that has been used frequently to assess PTSD risk among family  
810 members of critically ill patients.
- 811 9. Healthcare system distrust: The Healthcare System Distrust Scale will be used to assess  
812 two primary domains of distrust in healthcare (values and competence). This scale will  
813 be used to explore if distrust of the healthcare system has a mediating effect on  
814 surrogate outcomes, such as their perceptions of quality of death and dying and post-  
815 traumatic stress.

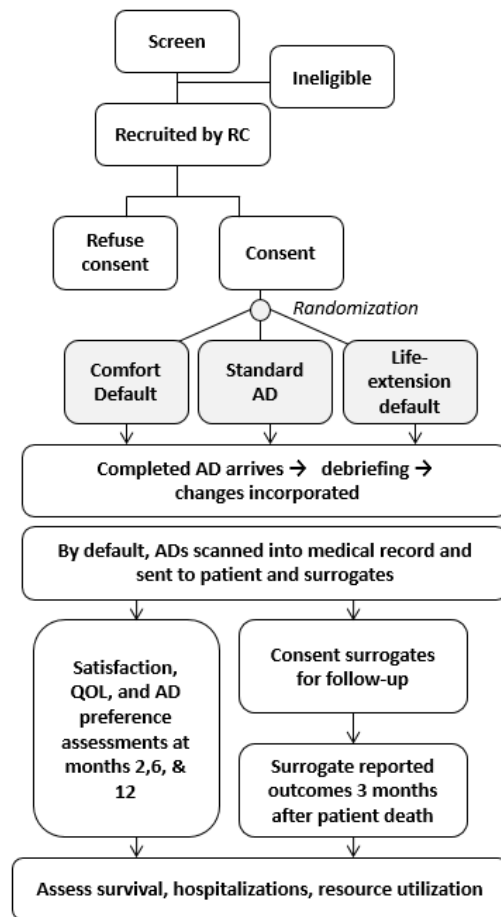
816

## 817 **4. Study Design**

### 818 **4.1 Schema**

819 This is a prospective, randomized, controlled trial.





820

821 **4.2 Duration**

822 The study period extended to 34 months. Subjects were accrued over a period of 27 months  
 823 starting in February 2014. The total time it will take for the research coordinator to explain the  
 824 study, obtain consent and for a subject to complete the advance directive will, conservatively,  
 825 take no more than two hours. The debriefing discussion and follow up interviews will take  
 826 approximately 15 – 25 minutes each. The total time spent on research activities for patients  
 827 should be no more than 4 hours.

828 **5. Subject recruitment**

829

830 We will recruit 270 patients with severe respiratory, oncological, neuromuscular, or  
 831 cardiovascular diseases and limited life expectancy from the Perelman Center for Advance Care  
 832 Medicine, Penn Presbyterian Medical Center, Pennsylvania Hospital, and the University of  
 833 Pittsburgh Medical Center. Each week the research coordinators will screen the electronic  
 834 medical records of patients scheduled for routine visits to determine their study eligibility using  
 835 the eligibility criteria outlined above.

836 Once eligible patients have been identified, research coordinators will email eligible patients'  
837 providers to 1) alert them to their patients' eligibility for participation 2) inform them their  
838 patients will be recruited for enrollment 3) provide them an opportunity to decline or defer any  
839 given patient's enrollment by responding to the email. Research coordinators will approach  
840 potential study participants while they are in the waiting areas, chemotherapy infusion areas,  
841 or in exam rooms waiting to see their doctor on the day of their visit.

## 842 **5.1 Accrual**

843  
844 During our pilot study we were able to recruit approximately six patients per month with one  
845 full-time research coordinator. We anticipate that with the equivalent of 3.5 full-time research  
846 coordinators and an additional site (University of Pittsburgh), we will be able to recruit  
847 approximately 18 patients per month.

## 848 **5.2 Key inclusion criteria**

849  
850 The eligibility criteria, all of which must be met, are:

- 851 1. Age 18 or older
- 852 2. Speaks and reads fluent English
- 853 3. Has seen current physician at least once prior to current visit
- 854 4. Resident of Pennsylvania or New Jersey
- 855 5. One or more of the following diagnoses:
  - 856 • Amyotrophic lateral sclerosis
  - 857 • Stage IIIB or IV non-small cell lung cancer or cholangiocarcinoma
  - 858 • Stage IV colorectal, esophageal, gastric (including GIST), pancreatic, prostate, uterine,  
859 cervical, ovarian or urothelial cancer; paraganglioma, or pheochromocytoma
  - 860 • Stage C or D hepatocellular carcinoma
  - 861 • Stage IV renal cell carcinoma
  - 862 • Stage IV or V chronic kidney disease
  - 863 • Mesothelioma or any malignancy metastatic to the pleura
  - 864 • Other incurable interstitial lung diseases with at least severe restriction on most recent  
865 pulmonary function tests or eligible for long-term oxygen therapy
  - 866 • Chronic obstructive pulmonary disease with at least severe airflow obstruction on most  
867 recent spirometry or eligible for long-term oxygen therapy
  - 868 • Congestive heart failure with NYHA Class IV status or Class III plus 1 heart failure-related  
869 hospitalization in the past 12 months or ACC stage D or C classification with 1 heart  
870 failure-related hospitalization in the past 12 months
  - 871

- 872       • Stage IV breast cancer except patients whose only metastases are to the bones or who  
873       are receiving endocrine therapy without receiving concomitant traditional  
874       chemotherapy

### 875   **5.3 Key exclusion criteria**

876  
877 Patients will be excluded if they are currently listed for or being considered for solid organ  
878 transplant and if they have a previously signed advance directive or living will. Cognitively  
879 impaired patients will be excluded from the study to avoid the necessity of proxy consent.

### 880   **5.4 Subject Remuneration**

881  
882 Patients will be compensated with a \$20 Amazon.com gift card following completion of the  
883 debriefing session. In order to enhance study retention and participation in follow-up  
884 assessments, a \$20 Amazon.com gift card will also be given to subjects at the completion of the  
885 two, six, and twelve month follow-ups. Surrogates will also be compensated with a \$20  
886 Amazon.com gift card after they consent to participate.

## 887   **6. Randomization**

888

### 889   **6.1 Groups**

890

891 Subjects enrolled in this RCT will be randomized into three groups. Depending on which group  
892 they've been assigned, subjects will be given one of three AD forms. The three AD forms have  
893 been created with different default treatment options. Form 1 (life-extension default) will state  
894 that 4 specific life-extending interventions (cardiopulmonary resuscitation, mechanical  
895 ventilation, hemodialysis, and feeding tube insertion) will be provided unless patients  
896 specifically opt-out from such selections. Form 2 (comfort default) will state that the 4 specific  
897 life-extending interventions will not routinely be provided unless patients elect to receive such  
898 measures. Finally, Form 3 (standard advance directive) will use the standard approach of  
899 requiring patients to actively choose whether or not they wish to receive each intervention, as  
900 they would if completing an AD outside of a research setting. In this case, if they do not make a  
901 selection, decision making would default to their surrogates as in usual practice.

902

903 Because patients may focus on an overall plan of care rather than the receipt of specific  
904 interventions, all AD forms will also include a general question regarding treatment priorities.  
905 The response to this question, is modeled on one used in a Study to Understand Prognoses and  
906 Preferences for Outcomes and Risks of Treatments (SUPPORT) study. The question  
907 acknowledges that while, in general, most people wish to both live as long as possible and avoid

908 pain and suffering, in some situations, choosing between these two goals may be necessary. It  
909 then asks patients, if they are in a situation where such a choice is needed, whether they prefer  
910 a plan of care that focuses on extending life as much as possible even if it means having more  
911 pain and suffering, or a plan of care that focuses on relieving pain and suffering even if that  
912 means not living as long. The default framing of this general question will be in accord with that  
913 used for the specific interventions in each AD form, and all patients will be able to select a “no”  
914 option in response to this question.

915

916 Finally, we will include a specific question about the care patients wish to receive upon  
917 discharge from the hospital, defaulting to hospice-based care (in the comfort-default group),  
918 long-term care (in the life-extension-default group), or no option pre-selected. In the standard  
919 AD group, although no options will be pre-selected, we will randomly assign whether the  
920 comfort-oriented option or the life-extending-oriented option is presented first so as to  
921 mitigate ordering effects. In all cases, the option of not deciding will be presented last.

## 922 **6.2 Assignment**

923

924 Eligible patients will be approached about participation by the research coordinators in the  
925 outpatient clinics at the Perelman Center for Advanced Medicine, Pennsylvania Hospital, and  
926 Presbyterian Hospital. Consenting subjects will be randomized with a 33.3% probability to each  
927 trial arm (life extension default, comfort default, standard AD) using electronic procedures  
928 monitored by the Data Management Unit within the Biostatistics Analysis Center. We will  
929 stratify the randomization by recruiter/research coordinator, and will use variable block sizes of  
930 3 and 6 patients to promote balance of follow-up duration among the 3 trial arms.

931

932 Each research coordinator will go to his or her clinics each day with a sealed envelope in which  
933 there is a pre-determined sequence of the 3 trial packets. The research coordinator will become  
934 unblinded to the patient’s allocation at the time of consent, but with variable block sizes, can  
935 never predict with certainty what the next packet will be.

## 936 **7. Study Procedures**

937

### 938 **7.1 Screening for Eligibility**

939

940 The research coordinators will screen electronic medical records of patients visiting pulmonary,  
941 renal, heart failure, movement disorder, and oncology clinics at the Perelman Center for  
942 Advance Care Medicine, Penn Presbyterian Medical Center, Pennsylvania Hospital and the  
943 University of Pittsburgh Medical Center for eligibility. Patient’s eligibility status will be entered

944 into the eligibility database. We will record ICD9 and ICD 10 codes, staging information,  
945 relevant provider name, clinic location, and upcoming appointments for eligible patients.

## 946 **7.2 Recruitment**

947  
948 Eligible patients will be approached by a research coordinator in the clinics who will seek  
949 patients' consent to participate in a study comparing different types of ADs. Of note, while  
950 some providers may be more proactive than others in engaging their patients in conversations  
951 about advance care planning, it is generally not standard-of-care that patients are approached  
952 about completing ADs. The research coordinator will specify that the ADs in this study are  
953 intended to be real ADs and that they will be included in patients' outpatient medical records,  
954 but that, as with all ADs, patients retain the right to change their selections at later dates. The  
955 research coordinator will also specify that, like all real ADs, they are most useful if copies are  
956 shared with their loved ones and physicians.

## 957 **7.3 Informed Consent**

958  
959 Following discussion of the study, research coordinators will obtain written consent from  
960 patients. The consent forms will contain HIPAA statements of authorization of release of  
961 medical records, thus facilitating our collection of data from medical and billing records during  
962 the study. The consent includes clear explanations that different types of ADs will be assigned  
963 by chance, but that patients in all groups may select or decline any intervention or treatment  
964 goal, and may revise their choices at any time. The research coordinators will explain who will  
965 be enrolled, how many patients are being targeted for enrollment, the specific components of  
966 patient follow-up, patients' rights to withdraw from the study at any time and for any reason,  
967 and what the outcomes of interest are (e.g., utilization of healthcare services, AD selections).  
968

## 969 **7.4 Enrollment**

970  
971 After patient consent is obtained, the research coordinator will ask subjects to complete the  
972 demographics survey, indicate whether they prefer to be contacted by phone or email, and  
973 walk subjects through the process of filling out the AD. Along with their AD forms, consenting  
974 subjects will be given a copy of their consent form, an informational brochure about advance  
975 care planning, contact information for research study staff, instructions for mailing back their  
976 completed AD forms, the decision conflict scale, and a stamped and addressed envelope. The  
977 DCS will be sent home with consenting patients to complete and return, along with an  
978 instruction sheet explaining to patients that they should complete their AD first, followed by  
979 the DCS.  
980

981 Subject IDs will be assigned at the point of consent. Subject ID numbers, demographic  
982 information and group assignments will be entered into the analytic database. Subject contact  
983 information, including social security number, will be entered into a subject tracking database.  
984

985 If completed ADs are not returned within 10 days, staff will call or email patients weekly to  
986 remind them to return their ADs, to schedule special clinic visits for AD completion if patients  
987 desire, and to answer any questions. If research staff members are unable to reach patients  
988 over the phone or email after three attempts, a letter will be sent to patients to remind them to  
989 return their ADs and encourage them to contact research staff if they have any questions or  
990 difficulties. If we are still unable to reach patients, they will be approached by the research  
991 coordinator at their next clinic visit.  
992

### 993 **7.5 Subject Debriefing**

994

995 After patients complete their assigned AD, there will be a structured debriefing session  
996 conducted over the phone, regardless of patients' preferred contact method, by a research  
997 team member in which a standardized explanation of all three ADs will be given. If the patient is  
998 unable to be reached by phone, they will be approached at their next clinic visit to complete  
999 the debriefing in person. This debriefing will be held to alert patients to exactly how the three  
1000 ADs used in the study differ. As in the pilot study, patients will not be alerted to the different  
1001 default framings up front because patients in clinical settings (and indeed in this study) are only  
1002 asked to complete a single AD. Explaining non-relevant ADs prior to completion of the relevant  
1003 one could influence decisions in ways that would not reflect actual clinical settings, thereby  
1004 biasing the results. However, because this is a research study and AD assignment is at random,  
1005 it is appropriate to debrief patients afterwards to grant them such broader information. Once  
1006 patients are fully informed about the variations in the ADs used in the study, they will be asked  
1007 if they wish to change any of their AD selections prior to finalizing the documents as a part of  
1008 the medical record. Patients who choose to make changes to their AD's during the debriefing  
1009 can choose to have their original AD sent back to them along with a blank AD to complete and  
1010 return, or the research team will make the changes directly on the AD forms and send a letter  
1011 back to the patient indicating the changes have been made and instructing the patients to call  
1012 the research team if they do not approve of the changes and/or would like additional changes.  
1013 If we do not hear from the patients within 10 days, the study team will consider the revised AD  
1014 complete. Patient ADs will not be considered "complete" until the debriefing session has taken  
1015 place. After the debriefing call, patients' AD selections will be entered into the analytic  
1016 database.  
1017

1018 During the debriefing call, we will tell subjects that we will scan their AD forms into their  
1019 medical records for them, unless they do not desire this (it is optional, not a requirement of the  
1020 study). Similarly, we will also inform subjects that a copy of their completed AD will be sent  
1021 back to them along with a \$20 Amazon.com gift card as compensation for their time, and that,  
1022 if they wish, a copy will be sent to their appointed healthcare agent/surrogate. Completed ADs  
1023 will be sent to patients and surrogates along with letters explaining that ADs can be changed at  
1024 any time and they can contact the research team with questions.

1025  
1026 Research coordinators will help facilitate the scanning of patients' completed ADs into their  
1027 medical records, for patients who wish to do so. Completed ADs will be given to clinic  
1028 administrative staff along with a step by step instruction sheet explaining that we are asking  
1029 that the AD be scanned into the patient's medical record and where, in the medical record, the  
1030 ADs should be placed. Two weeks after the completed ADs have been delivered to clinic staff,  
1031 the research coordinators will review the medical record in Epic to confirm the successful  
1032 upload of the documents. In addition, a confirmation email will be sent to patients' physicians  
1033 informing them that their patients have active ADs as part of their medical record.

1034

## 1035 **7.6 Subject Follow-up**

1036

1037 Two, six, and twelve and months after AD completion, subjects will be contacted for  
1038 participation in follow-up interviews. The follow-up interviews will take place over the phone  
1039 with a research associate blinded to the subject's study arm, or online through REDCap,  
1040 depending on the patient's preferred method of communication. The research associates will  
1041 attempt to contact patients up to two times using their preferred method of communication. If  
1042 the two first attempts are unsuccessful, we will attempt to contact the patient using the  
1043 alternate method. If we are unable to reach the patient following the third attempt, we will  
1044 scan EPIC for the patient's next in-clinic appointment, during which a research coordinator,  
1045 blinded to the patient's study arm will attempt to complete the follow-up interview in person.  
1046 In advance of this in-person meeting, we will send a letter to the patient notifying them of our  
1047 efforts to reach them, and indicate a member of our study team would like to meet with them  
1048 during their next clinic visit. If patients are unavailable to participate in follow-up calls because  
1049 they are deceased or otherwise incapacitated, we will interview their surrogates.

1050

1051 Prior to contacting patients for follow-up assessments, we will screen their EPIC medical  
1052 records to check patient mortality. EPIC will capture the vast majority of deaths within 2-3  
1053 weeks, as mortality data are entered by clinic staff in regular contact with seriously ill patients.

1054

1055 **7.7 Assessment of Health Outcomes**

1056  
1057 We will assess hospitalizations, ICU admissions, costs of inpatient care, and utilization of life-  
1058 sustaining therapies by querying state-run databases that capture all admissions and inpatient  
1059 procedures in Pennsylvania and New Jersey. The Pennsylvania Health Care Cost Containment  
1060 Council (PHC4) is an independent state agency that maintains a database of inpatient hospital  
1061 discharge and outpatient procedure records from all hospitals and ambulatory surgery centers  
1062 in Pennsylvania. These data include specific treatment information including costs. As roughly  
1063 one-third of Penn’s outpatient population resides in New Jersey, we will obtain comparable  
1064 data from the New Jersey Discharge Data Collection System (NJDDCS) managed by the New  
1065 Jersey Department of Health and Senior Services within their Department of Health Care  
1066 Quality and Assessment (HCQA). We will establish data use agreements with both of these  
1067 entities and be subject to IRB approval by HCQA. Linkages with both PHC4 and NJDDCS will be  
1068 performed by the respective database administrators after we provide lists of included social  
1069 security numbers and subject IDs. PHC4 and NJDHSS will send our team a report in which  
1070 patients are identified by subject ID only. Identical processes have been used seamlessly and  
1071 with high fidelity by many Penn investigators.

1072

1073 **8. Data Management**

1074 **8.1 Data Confidentiality**

1075  
1076 Only authorized project personnel will have access to the data. All study data will be stored  
1077 behind firewalls on Center for Clinical Epidemiology and Biostatistics (CCEB) servers; none will  
1078 be stored on stand-alone PCs or laptops. All study personnel who work with these data will  
1079 have undergone required human subjects training. To ensure that participant confidentiality is  
1080 preserved, individual identifiers (such as social security number) will only be used to link patient  
1081 records (e.g., linking subject database to PHC4 data). Once linkages between databases have  
1082 been achieved, all linkage-identifiers will be dropped from all datasets. Throughout the study  
1083 duration, we will maintain one master list that will link study identification numbers to patient  
1084 identifiers. This list will be maintained by the principal investigator in a locked file drawer in his  
1085 locked private office to ensure file security. This file will be made available to other research  
1086 staff on a need-to-know basis only, and, in that case, only temporarily. The study ID will be used  
1087 exclusively in all analytical files.

1088

1089 We will implement multiple, redundant protective measures to guarantee the privacy and  
1090 security of the participant data. All data for this project will be stored on the secure/firewalled  
1091 servers of the CCEB in data files that will be protected by multiple password layers. These data



1092 servers are maintained in a guarded facility behind several locked doors, with very limited  
1093 physical access rights. They are also cyber-protected by extensive firewalls and multiple layers  
1094 of communication encryption. Electronic access rights are carefully controlled by Penn system  
1095 managers. We will use highly secure methods of data encryption for all transactions involving  
1096 participants' financial information using a level of security comparable to what is used in  
1097 commercial financial transactions. This multi-layer system of data security, identical to the  
1098 system protecting the University of Pennsylvania Health System's medical records, greatly  
1099 minimizes privacy risks.

## 1100 **8.2 Subject Confidentiality**

1101  
1102 Steps will be taken to ensure that all information will be kept confidential and secure. Unique  
1103 patient identifiers numbers will be assigned to each subject locally and kept in a secure  
1104 encrypted file. Records with patient social security numbers will be maintained, used, and  
1105 destroyed in a way that is consistent with Penn policy. All paper records will be kept in locked  
1106 files; all computers will be password protected and kept in locked rooms; all databases will be  
1107 password protected and maintained on encrypted hard-drives behind the CCEB firewall. All  
1108 study data will be stored behind firewalls on Center for Clinical Epidemiology and Biostatistics  
1109 (CCEB) servers; none will be stored on stand-alone PCs or laptops. All data will be destroyed  
1110 after 7 years.

## 1111 **8.3 Subject Privacy**

1112  
1113 Individual-level data for participants will be kept confidential and will only be stored on highly  
1114 secure servers available for patient-level data. Only authorized project personnel will have  
1115 access to the data and the data will be stored on servers only and not stand-alone PCs or  
1116 laptops. All study personnel who work with subject identifiers and contact information will have  
1117 undergone all required human subjects training. They will work with the data in password  
1118 protected files and once enrollment and follow up are complete, all identifying information will  
1119 be removed. Personally identifiable information will NOT be included in the analytic database.

1120  
1121 Potential subjects will be approached, in clinics, by highly trained research staff members who  
1122 understand the importance of subject privacy. In most cases, the initial encounter with patients  
1123 will take place in private exam rooms or infusion suites. Potential subjects may be approached  
1124 in waiting areas, but it will be done in a way that is sensitive to maintaining privacy.

1125  
1126 Follow-up phone calls will be conducted by trained research staff who will be calling, primarily,  
1127 from their offices in Blockley Hall. Efforts will be made to ensure that phone calls will not be  
1128 overheard by anyone who is not directly involved with the research. In the event that research

1129 staff member needs to leave a voicemail message for a subject, they will do so in a way that  
1130 maintains subject privacy.

## 1131 **9. Data and Safety Monitoring**

### 1132 **9.1 Monitoring Plan**

1133  
1134 The data and safety monitoring plan will have 3 parts. First, the BECC will implement methods  
1135 of validating entered data, as they have done for numerous trials before, thereby ensuring the  
1136 quality of our data. Second, the PI will be directly responsible for identifying and reporting all  
1137 serious adverse events, protocol deviations/violations, and unanticipated events to the IRBs  
1138 and funding agency promptly, as appropriate. He will also report all adverse events, accrual  
1139 rates, retention rates, mortality/survival data and all other logistical issues to the DSMB at least  
1140 biannually (and more frequently as requested or needed). Third, we have convened a DSMB  
1141 that will be responsible for monitoring the trial and making decisions about the termination of  
1142 individual study arms or the study itself.

1143  
1144 The DSMB will consist of individuals with considerable expertise in human subjects research,  
1145 vulnerable populations, bioethics, clinical trials, decision making, palliative care, and  
1146 biostatistics. The PI (Dr. Halpern), the project manager (Elizabeth Cooney), and the lead  
1147 statistician (Dr. Troxel), will participate in all DSMB meetings as non-voting members. The PI,  
1148 assisted by the project manager, will be responsible for maintaining communication between  
1149 the DSMB and the individual project staff.

1150  
1151 The DSMB will perform several duties. First, they will review and approve the research protocol  
1152 and plans for data and safety monitoring. Second, they will evaluate the progress of the trial.  
1153 This will include assessment of data quality, participant recruitment, accrual and retention,  
1154 participant risk versus benefit, and study outcomes. This assessment will be performed at  
1155 meetings every 6 months during the study and more frequently if needed. They will be paying  
1156 particularly close attention to patient survival as well as selections made on advance directive  
1157 forms. Third, they will make recommendations to ensure that all of the issues above are  
1158 appropriately addressed. Dr. Halpern, as the study PI, will be responsible for responding to all  
1159 recommendations of the DSMB and submitting DSMB reports to the Penn and Pitt IRBs.

### 1160 **9.2 Data Safety Monitoring Board Members**

1161  
1162 The DSMB has been constituted and includes the following members:

- 1163  
1164 1. David Wendler, PhD: expertise in research with vulnerable populations and research  
1165 ethics, including the role of debriefing in RCTs.

- 1166 2. Vicki Jackson, MD, MPH: expertise in palliative care for dying patients, and physician-  
1167 patient-family communication regarding end-of-life decisions.  
1168 3. Manisha Desai, PhD: expertise in statistical methods for the analysis of clinical trials,  
1169 including the implementation of stopping rules.  
1170

1171 The DSMB will also be responsible for reviewing the provided data at the 6 month and 1 year  
1172 interim analyses, determining the scientific validity and safety to determine whether the study  
1173 should be continued, and will advise the PI regarding whether to bring the project to a close.  
1174 The project manager, Elizabeth Cooney, and the staff analyst will assist Drs. Halpern and Troxel  
1175 in providing the DSMB with any additional information on request.

## 1176 **10. Human Subjects Protection**

### 1177 **10.1 Risk / Benefit Assessment** 1178

1179 This study presents no more than minimal risk. Many precautions will be taken to protect  
1180 subjects against the most likely risk which is breach of confidentiality. In addition, the ADs are  
1181 not legally binding and therefore are unlikely to erect barriers to patients receiving desired  
1182 care. Instead, the ADs may merely help them avoid unwanted treatments. As a result, the  
1183 potential benefits to individual subjects in terms of learning about ADs and to society from  
1184 learning about a scalable intervention to improve the uptake, patient-centeredness, and  
1185 effectiveness of advance directives far exceed the potential risk.  
1186

1187 The potential risks to human subjects in this research include (1) risks of breach of  
1188 confidentiality of personal health information (PHI), (2) risks of emotional distress brought on  
1189 by being asked to contemplate end-of-life care, and (3) risks that the interventions could have  
1190 untoward impacts on patients or their family members. Potential untoward impacts include  
1191 unfavorable changes in quality of life, duration of life, satisfaction with end-of-life care  
1192 planning, surrogate perceptions of the quality of dying and death, surrogate bereavement and  
1193 psychiatric disturbance following deaths of loved ones, or altering (increasing or decreasing)  
1194 utilization of interventions at the end of life in ways that patients would not prefer. Of note, we  
1195 anticipate favorable – or at worst neutral – impacts on each of these outcomes, but are  
1196 designing our study to detect and respond quickly to unforeseen negative impacts in any of  
1197 these domains.  
1198

1199 Participants in this study may benefit directly from the opportunities to discuss and clarify their  
1200 end-of-life care preferences with experienced personnel who can facilitate inclusion of these  
1201 preferences into their future clinical care. Participants also may benefit from the knowledge  
1202 that their surrogates have clear direction on their wishes and thus, may experience fewer

1203 burdens with difficult decision-making, perhaps alleviating subsequent stress or depression.  
1204 However, participants will be instructed that this is research, and like all research, it is being  
1205 conducted with the primary goal of producing generalizable knowledge. Thus, the primary  
1206 benefits to be gained are those related to the knowledge to be gained.

1207  
1208 The knowledge to be gained in this study may be of considerable importance. Given the  
1209 widespread dissatisfaction with the quality of end-of-life care in the U.S., this randomized trial a  
1210 readily scalable intervention to improve the uptake, patient-centeredness, and effectiveness of  
1211 advance directives, which stems from a novel and innovative conceptual framework, holds  
1212 great promise for improving public health. The simple and inexpensive methods to be tested  
1213 may go a long way towards narrowing the gap between the care patients prefer near the end of  
1214 life and the care they actually receive.

## 1215 **10.2 Protective Measures**

1216  
1217 The first safeguard for protection of human subjects includes an experienced and well-trained  
1218 study team. Dr. Scott Halpern (PI) is the Principal investigator. He has substantial experience  
1219 conducting RCTs of behavioral economic interventions to modify health-related behaviors, in  
1220 the ethics of applying behavioral economics to health decisions, and in the design, ethics, and  
1221 recruitment barriers of RCTs. As Principal Investigator for the proposed trial, Dr. Halpern will be  
1222 primarily responsible for the completion of all aspects of this RCT including study design,  
1223 underlying data infrastructure, compliance with IRB requests and requirements, participant  
1224 recruitment, data collection and management, data analysis, adherence to all policies and  
1225 procedures for clinical research.

1226 Collaborating with Dr. Halpern as co-investigators and overseeing recruitment at the University  
1227 of Pittsburgh are Drs. Cindy Bryce and Doug White. Dr. Bryce is a health services researcher  
1228 who has spent considerable time investigating the use of decision science to improve medical  
1229 decision-making in the context of critical illness. In addition to overseeing the implementation  
1230 of this study at Pitt, she brings her expertise as an investigator in preference-based assessment  
1231 of quality-of-life, cost effectiveness analysis, and behavioral decision theory for understanding  
1232 patient and surrogate decision making. Dr. White directs the University of Pittsburgh Program  
1233 on Ethics and Decision-Making in Critical Illness, which encompasses both empirical research  
1234 on, and normative ethical analysis of decision-making for, patients with life-threatening illness.  
1235 He will work with Dr. Bryce in coordinating the logistics and oversight of the study at Pitt and  
1236 will assist Dr. Halpern's team at Penn in interpreting results and preparing manuscripts related  
1237 to his area of particular expertise – surrogate decision-making.

1238 All study team members have completed training in HIPAA regulations and human subjects  
1239 research.

1240 The debriefing process is an important element of human subjects protection. It will ensure  
1241 that patients (1) understand their selections on their AD forms; (2) do not simply go with the  
1242 default options because they failed to recognize that a choice was to be made or that a default  
1243 was being used; (3) have multiple opportunities to withdraw their participation or data; and (4)  
1244 are actively engaged in the research and comfortable with the research process.

1245 Additional layers of protection for human subjects include the robust informed consent process  
1246 (section 7.3), exceptional data security (sections 8.1, 8.2 & 8.3), and the empowered Data  
1247 Safety and Monitoring Board (sections 9.1 & 9.2), all described in detail in this protocol.

### 1248 III. Summary of Changes

1249 The following changes to the protocol were made after the original protocol had been finalized on  
1250 January 09, 2014 and patient enrollment had begun on February 6, 2014.

- 1251 1. The study's enrollment period was originally planned for 18 months. Due to slower than expected  
1252 accrual, regulatory delays, and turnover of research staff the enrollment period lasted 27 months  
1253 (February 2014 – April 2016)
- 1254 2. We abandoned efforts to enroll patients who declined participation into the registry after roughly  
1255 20% of the sample had been enrolled due to low interest in the registry from patients. The purpose  
1256 of the registry was to enable outcomes to be collected among a broader group of patients who did  
1257 not complete ADs, thereby enabling complier average treatment effect analyses of patients' quality  
1258 of life. This goal would only be enabled with nearly complete accrual of non-enrolled patients into  
1259 the registry. This proved infeasible early on.
- 1260 3. Submitted to the IRB 03.31.14 – For ease of use and risk management reasons we changed patient  
1261 remuneration for completion of follow-up assessments to amazon.com gift cards instead of cash.
- 1262 4. Submitted 04.23.14 – In order to ease the burden of a lengthy assessment for bereaved family  
1263 members we eliminated the use of Prigerson's Complicated Grief Inventory and the Quality of Death  
1264 and Dying Instrument. We replaced these instruments with Prigerson's Quality of Death measure.
- 1265 5. Submitted 09.08.13 – We added specificity around the timing and frequency of follow-up calls to  
1266 patients to encourage them to return their completed AD within 30 days. We also expanded  
1267 eligibility criteria to include patients with Stage IV uterine, cervical, and ovarian cancer.
- 1268 6. Submitted 04.28.15 – We added procedures to ensure and confirm AD upload in patients' medical  
1269 records including 1) an instruction sheet for clinical staff indicating where ADs should go in the  
1270 medical record and 2) a protocol to confirm presence of an AD in the record within 2 weeks.
- 1271 7. Submitted 05.22.15 – We modified our demographics form to collect patients' email addresses and  
1272 ask patients if they prefer email vs. phone call follow-up. Additionally, we modified follow-up  
1273 procedures to allow for electronic survey completion of follow-up measures. We also added in-  
1274 person completion of follow-up measures in outpatient clinics. We also modified the timing of

1275 patient remuneration such that patients would receive their first \$20 gift card after AD completion  
1276 instead of at the point of consent.

1277 8. Submitted 12.22.15 – Due to low response rate and resource constraints we eliminated collection of  
1278 follow-up measures for patients who did not complete ADs.

1279 9. Submitted 07.20.16 – Due to observation, in preparation for a DSMB meeting, of missing  
1280 demographic data, we obtained permission from the IRB to manually search the electronic health  
1281 records to improve demographic data completeness.

1282 **No further changes to the protocol were made after this ninth modification. Thus, the**  
1283 **protocol was considered finalized after receiving IRB approval for the final modification on**  
1284 **August 10, 2016.**

1285 |

1286

## 1287 IV. Original Statistical Analytic Plan

1288

### 1289 **1. Analytic Methods**

1290 To assess balance among groups achieved by randomization, we will compare baseline values of all  
1291 variables across arms using ANOVA and chi-square tests for continuous and binary data, respectively.  
1292 We will use Poisson models to assess the number of hospital free days (HFDs) from the time of  
1293 randomization. We will use logistic, linear, or quantile (1) regression, as appropriate based on outcome  
1294 parameterizations and distributions, for all secondary outcomes. In all analyses, we will model the clinic  
1295 from which patients are recruited as a random effect to adjust for potential clustering within clinics and  
1296 to mitigate confounding by clinic (2). We will employ standard covariate-selection procedures for  
1297 etiologic models to assess, and potentially adjust for, chance covariate imbalance among arms.  
1298 Specifically, patient-level covariates (e.g., gender, race, diagnosis category) will be included in  
1299 multivariable models based on pre-specified hypotheses or if their inclusion – singly or jointly – modifies  
1300 the coefficient for the randomized exposure by  $\geq 15\%$  (3).

1301

1302 All analyses will be conducted using the intention-to-treat approach to avoid selection bias. Some  
1303 patients who consent to participate and receive their assigned AD may not return the AD. In our pilot  
1304 work we developed several interventions that successfully mitigated this possibility. However, any  
1305 patients who do not return the AD will be retained in the primary analyses, and will be classified as  
1306 having not specified preferences for goals of care or specific interventions.

1307

### 1308 **2. Specific aims and hypothesis**

1309 (a) ADs with preselected comfort care options, compared with those defaulting to life-  
1310 extension or standard ADs, will produce an increase in hospital-free days (HFDs), a measure  
1311 that represents the number of days alive and not in an acute care facility.

1312 (b) Compared with standard ADs or ADs defaulting to life-extension, ADs defaulting to comfort  
1313 care will:

- 1314 1. produce no change in survival
- 1315 2. reduce hospital and ICU admissions
- 1316 3. reduce costs of inpatient care
- 1317 4. improve patients' quality of life
- 1318 5. improve patients' satisfaction with end-of-life care and decision making
- 1319 6. improve surrogates' perceptions of the quality of dying and death
- 1320 7. decrease the incidence of symptoms of post-traumatic stress among surrogates  
1321 following their loved ones' death

### 1322 **3. Exposure**

1323 Intervention group (standard AD, life-extension default, or comfort care default)

1324

1325

## 1326 **4. Outcomes**

### 1327 **4.1 Primary**

1328 Primary outcome is Hospital-free days (HFD). This metric represents the number of days alive and not in  
1329 an acute care facility following the date of consent. We chose the date of consent as day 0 so that all  
1330 enrolled participants, including those who do not return ADs, are eligible for ITT analyses.

1331 The choice of HFDs as the primary outcome reflects the desire to choose a measure that is patient-  
1332 centered, readily measured and analyzed, and reflects a patient's holistic state rather than a specific  
1333 symptom. HFDs have many attractive properties: they are continuous, enhancing power; they can be  
1334 analyzed reliably and flexibly, to account for different values patients may place on avoiding  
1335 hospitalization; and in nearly all cases, they are unidirectional, in the sense that nearly all patients prefer  
1336 longer lives to shorter ones, and to have more of those days spent outside a hospital than within.

### 1337 **4.2 Secondary**

1338 Secondary outcomes include several clinical, economic and patient-reported measures including:

- 1339 1. Survival – Patient deaths will be captured via medical records and verified by the Pennsylvania  
1340 and New Jersey Departments of Health vital statistics
- 1341 2. Hospital and ICU admission – Captured by querying state-run databases that capture all  
1342 admission and inpatient procedures in Pennsylvania and New Jersey.
- 1343 3. Inpatient care charges – Captured via the database detailed in (2).
- 1344 4. Hospice utilization – Captured via data use agreements with Wissahickon hospice and Family  
1345 Hospice and Medical Care, organizations the provide care for 80% of eligible patients at Penn  
1346 and Pitt.
- 1347 5. Receipt of life-sustaining therapies – Captured via the database detailed in (2).
- 1348 6. Concordance between patients' expressed desires in ADs regarding four potentially life-  
1349 sustaining therapies (CPR, mechanical ventilation, dialysis, and feeding tube) and care received
- 1350 7. Quality of life – Measured at 2, 6, and 12 months following AD completion with the McGill  
1351 quality of life (MQOL), which can be completed by family members on behalf of patients who  
1352 are unable to complete it themselves. MQOL during follow-up is missing for a high number of  
1353 participants. In examining the data over time, we were able to determine that MQOL does not  
1354 change over time and that time to follow-up is not significantly related to MQOL values.  
1355 Therefore, we will only report one MQOL score per patient (in the per protocol analysis), and  
1356 this score will be the one closest to the 6 month follow-up period. Also, per-protocol patients  
1357 who die are assigned a value of 0 and the remainder are imputed.
- 1358 8. Satisfaction with advance care planning – Measured at 2, 6, and 12 months following AD  
1359 completion with the Canadian Healthcare Evaluation Project (CANHELP) instrument's global  
1360 satisfaction and end-of-life care question.
- 1361 9. Satisfaction/conflict with decision-making – Measured immediately following AD completion  
1362 using the validated decision conflict scale (DCS).



1363 10. Surrogates' perceptions of the quality of dying and death – Measured using Prigerson's quality  
1364 of death measures.

1365 11. Symptoms of post-traumatic stress among surrogates following their loved ones' death –  
1366 Measured using the Impact of Events Scale.

## 1367 **5. Analysis**

1368 We aim to answer two primary questions in this study:

1369 (1) What is the overall effectiveness of offering people the opportunity to complete advance  
1370 directives with different embedded default options?

1371 (2) What are the specific effects of making certain choices within ADs on patient and caregiver  
1372 outcomes?

1373 The primary way we'll answer question (1) is through the modified ITT analysis; question (2) will be  
1374 answered using a complier average treatment effect (CATE) analysis.

### 1375 **5.1 Modified ITT**

1376 The unit of analysis for the primary outcome (HFDs) will be the individual patient. mITT analyses include  
1377 all patients except for (1) post-randomization ineligible; (2) withdraws; and (3) patients who died within  
1378 30 days of randomization. The rationale for these exclusions is that none of these patients were fully  
1379 eligible to complete the assigned intervention in a way that would be accessible to the investigators.  
1380 Further, as expected, these losses are evenly distributed across the 3 arms (see CONSORT diagram) such  
1381 that their exclusion could not affect the results. In primary analyses, only patients who return an AD and  
1382 are debriefed will be counted as having returned an AD. In secondary analyses, all patients who return  
1383 ADs, regardless of debriefing status, will be included. mITT analyses will be conducted using linear  
1384 regression, adjusting for center, to compare the effects of assignment to complete ADs with different  
1385 default options on HFDs. This approach will use data from all randomized patients and will provide the  
1386 truest test of the overall effectiveness of the intervention among those randomly assigned to receive it.

### 1387 **5.2 CATE analysis**

1388 This analysis examines the effects of making certain choices within ADs on outcomes and accounts for  
1389 tendencies to not complete ADs. The CATE analysis surmounts the selection effects inherent in per-  
1390 protocol analyses, as well as the inability of ITT analyses to provide specific tests of the effects of choices  
1391 made in ADs because these effects will be diluted by the fact that many randomized patients will not  
1392 complete their assigned ADs. The CATE approach entails a two-stage least-squares regression in which  
1393 the randomization arm is modelled as an instrumental variable (IV) in complier average treatment effect  
1394 (CATE) analysis. This analysis will also be adjusted for center. Like the ITT analysis, these analyses use  
1395 data on all randomized patients to estimate the effects of specifying any treatment choice in ADs  
1396 regardless of group assignment, and after accounting for the possibility that AD completion rates may  
1397 differ among the three arms by using the randomization arm as the IV. Thus, the estimated effect of the  
1398 choices patients make is adjusted for the percentage of assigned patients who complete an AD at all,  
1399 and the percentage who opt out from their assigned default option. This IV uses data on all randomized  
1400 patients and then adjusts for AD completion rates, thereby attenuating the selection effects.

1401 This analysis also requires the use of principal stratification methods to formulate the causal quantities  
1402 of interest and determine the proportions of patients in each arm who would choose comfort care if  
1403 they were assigned to complete each version of the AD. The analysis assumes that all patients who  
1404 would choose comfort care in a standard AD would also choose it in an AD that defaults to comfort care,  
1405 and that all patients who would choose comfort care in an AD that defaults to aggressive care would  
1406 also choose it in a standard AD or an AD the defaults to comfort care. Coupled with the possibilities that  
1407 some participants would never return an AD, and that others would return an AD but not choose  
1408 comfort care regardless of group assignment, this creates five compliance classes (principal strata) of  
1409 participants. These classes are:

- 1410 i. Patients would not complete an AD regardless of group assignment
- 1411 ii. Patients would complete an AD but not choose comfort care regardless of group assignment
- 1412 iii. Patients would complete an AD and only choose comfort care if assigned to the comfort-  
1413 default AD
- 1414 iv. Patients would complete an AD and choose comfort care if assigned to the comfort-default  
1415 AD or standard AD
- 1416 v. Patients would complete an AD and choose comfort care regardless of group assignment

1417 Each patient has three potential outcomes (see below). Only one of the potential outcomes can be  
1418 observed, the outcome corresponding to the actual intervention the patient received. This is  
1419 represented by a binary endpoint – whether or not patients would have a high quality of life in the  
1420 future:

1421  $Y_i^A$  = whether patient  $i$  would have high quality of life if assigned to complete an aggressive-default AD  
1422  $Y_i^S$  = whether patient  $i$  would have high quality of life if assigned to complete a standard AD  
1423  $Y_i^C$  = whether patient  $i$  would have high quality of life if assigned to complete a comfort-default AD

1424 Our approach assumes the exclusion restriction that AD assignment only influences the potential  
1425 outcomes through the causal pathway of determining which type of care the patient chooses through  
1426 the AD. However, this assumption is likely to hold in this case, because the randomly assigned IV – which  
1427 of three versions of the AD is offered – would not influence outcomes unless it modified the probability  
1428 of AD completion or the choices made in the ADs.

### 1429 **5.3 Secondary analyses**

1430 Per-protocol analysis: The per-protocol analysis will compare patients who choose comfort care on their  
1431 ADs with patients who do not choose comfort care. Again, the main per-protocol analysis will only  
1432 include patients who return an AD and are debriefed, but an additional secondary analysis will be  
1433 performed that includes patients who return ADs and are not debriefed. This analysis will assess the  
1434 efficacy of an intervention among those who choose to accept it. However, it is important to recognize  
1435 that this analysis will likely be biased by selection effects because patients who complete ADs and  
1436 choose comfort care are likely different from those who do not complete ADs or make other choices in  
1437 completed ADs. These underlying differences may influence outcomes such as quality of life. We will  
1438 assess the magnitude of such selection effects by comparing results between the per-protocol, mITT,  
1439 and CATE analyses.

1440 Secondary outcomes analyses: Secondary outcomes will be analyzed using logistic, linear, or quantile  
1441 regression, as appropriate. The number of hospital and ICU admissions will be analyzed as count data.  
1442 Charges will be inflated to the date on which analyses are performed using the US gross domestic  
1443 product deflator.

1444

1445 In all models, center will be entered as a random effect to adjust for potential clustering within centers  
1446 and to mitigate confounding by clinic. Gender, race, and diagnosis category will be included in all  
1447 multivariable models based on pre-specified hypotheses, and others will be added if their inclusion –  
1448 singly or jointly – modifies the coefficient for the randomized exposure by  $\geq 15\%$ .

#### 1449 **5.4 Sensitivity analyses modifying the HFD calculation**

- 1450 a) We will recode the outcome as “Healthcare facility-free days”, which represent the number  
1451 of days alive where a patient is not in an acute care facility, a chronic care facility or a  
1452 nursing home will be evaluated as an alternative to hospital-free days  
1453 b) We will also analyze effects on the original “Hospital-free days” but only up through six  
1454 months of follow-up

#### 1455 **5.5 Subgroup analyses**

1456 Planned subgroup analyses will be conducted across groups defined by gender (male vs. female), age  
1457 (analyzed as a continuous variable), race (White vs. Black, excluding all other races), religion (Christian  
1458 vs. not Christian), diagnostic category (cancer vs. non-cancer), and the three prior experience questions.

#### 1459 **5.6 Mediator analysis**

1460 We will conduct three mediation analyses. First, the presence of an AD in the medical record (i.e., the  
1461 successful uploading of the completed AD to the patient’s medical record) will be examined as a  
1462 mediator variable for (1) the primary analysis examining the relationship between randomization group  
1463 and HFDs and (2) also for the secondary outcome of concordance of care. In addition, we will examine  
1464 (3) surrogates’ distrust of the healthcare system, measured by the Health System Distrust Scale, as a  
1465 mediating variable in the relationship between randomization group and surrogates’ perceptions of the  
1466 quality of death and dying.

1467 In order to establish a variable as a mediator, we will first confirm that the proposed mediating variable  
1468 precedes the outcome in time, and then conduct a series of regressions to evaluate the following four  
1469 hypotheses (presented for the primary analysis, below). Rejection of all four hypotheses is necessary to  
1470 establish the presence of an AD in the medical record as a mediator. These four hypotheses are:

- 1471 1. Randomization group has a significant effect on the presence of an AD in the medical record  
1472 2. Having an AD in the medical record has a significant effect on HFDs  
1473 3. Randomization group has a significant effect on HFDs  
1474 4. The effect of randomization group on HFDs is attenuated when the presence of an AD in the  
1475 medical record is added to the model

1476 Each hypothesis will be examined using linear or logistic regression, as appropriate, and will be adjusted  
1477 for center to account for any center differences.

1478 If the null hypothesis is rejected for the above four hypotheses, we will determine the proportion of  
1479 variability explained by the presence of an AD in the medical record by quantifying the change in the  
1480 treatment assignment coefficient between the reduced (#3 above) and full model (#4 above).

1481

## 1482 **6. Sample Size and Power**

1483 We calculate our sample size as that required to rule out a significant reduction in HFDs attributable to  
1484 random assignment to a default AD. This approach entails non-inferiority tests of data from a Poisson  
1485 distribution, such that we seek to reject the hypothesis of a rate ratio (RR) for HFDs that is significantly  
1486  $>1.0$ . By enrolling 270 patients who complete ADs—90 in each of the three arms—we will obtain at least  
1487 80% power to demonstrate non-inferiority up to a margin of an RR for HFDs  $\geq 1.18$  associated with use of  
1488 a default AD. This calculation is based on: (1) a one-sided  $\alpha$  of 0.05, yielding an upper confidence limit on  
1489 the observed RR that falls entirely below an RR of 1.18; (2) a mean number of HFDs in the control group  
1490 of 100, such that a RR of 1.18 would correspond to 15 (15%) fewer HFDs in a given AD group  
1491 ( $100/85=1.18$ ); (3) an allowance for considerable dispersion in the distribution of HFDs; (4) no loss to  
1492 follow-up because all deaths and hospitalizations will be checked against the Social Security Death Index  
1493 and Pennsylvania Health Care Cost Containment Council (PHC4), respectively; (5) an allowance for two  
1494 primary hypotheses tests (comparing both the comfort-default and life-extension default arms to the  
1495 control arm) and (6) a true RR of 1.0. This final choice reflects our hypothesis that assignment to all  
1496 three ADs will produce equivalent numbers of HFDs. If the true RR is below 1.0 (eg, the comfort default  
1497 increases HFDs), power would increase considerably. Further, because simulations used to generate  
1498 these sample size estimates included scenarios with extreme assumptions of data dispersion, and the  
1499 proposed sample sizes incorporate this conservative assumption, our observed power is likely to be  
1500 higher than stated.

1501 **This original Statistical Analysis Plan was finalized on March 18, 2014, after review and approval by**  
1502 **the DSMB during its first meeting.**

1503

## 1504 **V. Final Statistical Analytic Plan**

1505

### 1506 **1. Analytic Methods**

1507 To assess balance among groups achieved by randomization, we will compare baseline values of all  
1508 variables across arms using ANOVA and chi-square tests for continuous and binary data, respectively.  
1509 We will use Poisson models to assess the number of hospital free days (HFDs) from the time of  
1510 randomization. We will use logistic, linear, or quantile (1) regression, as appropriate based on outcome  
1511 parameterizations and distributions, for all secondary outcomes. In all analyses, we will model the clinic  
1512 from which patients are recruited as a random effect to adjust for potential clustering within clinics and

1513 to mitigate confounding by clinic (2). We will employ standard covariate-selection procedures for  
1514 etiologic models to assess, and potentially adjust for, chance covariate imbalance among arms.  
1515 Specifically, patient-level covariates (e.g., gender, race, diagnosis category) will be included in  
1516 multivariable models based on pre-specified hypotheses or if their inclusion – singly or jointly – modifies  
1517 the coefficient for the randomized exposure by  $\geq 15\%$  (3).  
1518

1519 All analyses will be conducted using the intention-to-treat approach to avoid selection bias. Some  
1520 patients who consent to participate and receive their assigned AD may not return the AD. In our pilot  
1521 work we developed several interventions that successfully mitigated this possibility. However, any  
1522 patients who do not return the AD will be retained in the primary analyses, and will be classified as  
1523 having not specified preferences for goals of care or specific interventions.  
1524

## 1525 **2. Specific aims and hypothesis**

- 1526 a) Compared with standard ADs, neither ADs with preselected comfort care options nor ADs with  
1527 preselected options intended to promote life extension will reduce patients' hospital-free days  
1528 (HFDs), a measure that represents the number of days alive and not in an acute care facility.  
1529 b) Compared with standard ADs or ADs defaulting to life-extension, ADs defaulting to comfort care  
1530 will:
- 1531 1. produce no change in survival
  - 1532 2. reduce hospital and ICU admissions
  - 1533 3. reduce costs of inpatient care
  - 1534 4. improve patients' quality of life
  - 1535 5. improve patients' satisfaction with end-of-life care and decision making
  - 1536 6. reduce the receipt of life-sustaining therapies

## 1537 **3. Exposure**

1538 Intervention group (standard AD, life-extension default, or comfort care default)

## 1539 **4. Outcomes**

### 1540 **4.1 Primary**

1541 Primary outcome is Hospital-free days. This metric represents the number of days alive and not in an  
1542 acute care facility following the date of consent. We chose the date of consent as day 0 so that all  
1543 enrolled participants, including those who do not return ADs, are eligible for ITT analyses.

1544 The choice of HFDs as the primary outcome reflects the desire to choose a measure that is patient-  
1545 centered, readily measured and analyzed, and reflects a patient's holistic state rather than a specific  
1546 symptom. HFDs have many attractive properties: they are continuous, enhancing power; they can be  
1547 analyzed reliably and flexibly, to account for different values patients may place on avoiding  
1548 hospitalization; and in nearly all cases, they are unidirectional, in the sense that nearly all patients prefer  
1549 longer lives to shorter ones, and to have more of those days spent outside a hospital than within.

### 1550 **4.2 Secondary**

1551 Secondary outcomes include several clinical, economic and patient-reported measures including:

- 1552 1. Survival – Patient deaths will be captured via medical records and verified by the Pennsylvania  
1553 and New Jersey Departments of Health vital statistics
- 1554 2. Hospital and ICU admission – Captured by querying state-run databases that capture all  
1555 admission and inpatient procedures in Pennsylvania and New Jersey.
- 1556 3. Total Inpatient care charges – Captured via the database detailed in (2).
- 1557 4. Inpatient care charges per day per visit- Captured via the database detailed in (2).
- 1558 5. Receipt of life-sustaining therapies – Captured via the database detailed in (2).
- 1559 6. Concordance between patients’ expressed desires in ADs regarding four potentially life-  
1560 sustaining therapies (CPR, mechanical ventilation, dialysis, and feeding tube) and care received
- 1561 7. Quality of life – Measured at around 6 months following AD completion with the McGill quality  
1562 of life (MQOL), which can be completed by family members on behalf of patients who are  
1563 unable to complete it themselves. MQOL during follow-up is missing for a high number of  
1564 participants. In examining the data over time, we were able to determine that MQOL does not  
1565 change over time and that time to follow-up is not significantly related to MQOL values.  
1566 Therefore, we will only report one MQOL score per patient (in the per protocol analysis), and  
1567 this score will be the one closest to the 6 month follow-up period. Also, per-protocol patients  
1568 who die are assigned a value of 0 and the remainder are imputed.
- 1569 8. Satisfaction with advance care planning – Measured at 2 months following AD completion with  
1570 the Canadian Healthcare Evaluation Project (CANHELP) instrument’s global satisfaction and end-  
1571 of-life care question.
- 1572 9. Satisfaction/conflict with decision-making – Measured immediately following AD completion  
1573 using the validated decision conflict scale (DCS).

## 1574 **5. Analysis**

1575 We aim to answer two primary questions in this study:

- 1576 (1) What is the overall effectiveness of offering people the opportunity to complete advance  
1577 directives with different embedded default options?
- 1578 (2) What are the specific effects of making certain choices within ADs on patient outcomes?

1579 The primary way we’ll answer question (1) is through the modified ITT analysis; question (2) will be  
1580 answered using a complier average treatment effect (CATE) analysis.

### 1581 **5.1 Modified ITT**

1582 The unit of analysis for the primary outcome (HFDs) will be the individual patient. mITT analyses include  
1583 all patients except for (1) post-randomization ineligibles; and (2) withdraws. The rationale for these  
1584 exclusions is that none of these patients were fully eligible to complete the assigned intervention in a  
1585 way that would be accessible to the investigators. Further, as expected, these losses are evenly  
1586 distributed across the 3 arms (see CONSORT diagram) such that their exclusion could not affect the  
1587 results. In primary analyses we include all patients regardless of AD return or debriefing.

1588 mITT analyses will be conducted using count regression, adjusting for center, to compare the effects of  
1589 assignment to complete ADs with different default options on HFDs. We found center and diagnosis are

1590 highly correlated and used diagnosis in the model building. This approach will use data from all  
1591 randomized patients and will provide the truest test of the overall effectiveness of the intervention  
1592 among those randomly assigned to receive it.

## 1593 **5.2 CATE analysis**

1594 This analysis examines the effects of making certain choices within ADs on outcomes and accounts for  
1595 tendencies to not complete ADs. The CATE analysis surmounts the selection effects inherent in per-  
1596 protocol analyses, as well as the inability of ITT analyses to provide specific tests of the effects of choices  
1597 made in ADs because these effects will be diluted by the fact that many randomized patients will not  
1598 complete their assigned ADs. The CATE approach entails a two-stage least-squares regression in which  
1599 the randomization arm is modelled as an instrumental variable (IV) in complier average treatment effect  
1600 (CATE) analysis. This analysis will also be adjusted for center. Like the ITT analysis, these analyses use  
1601 data on all randomized patients to estimate the effects of specifying any treatment choice in ADs  
1602 regardless of group assignment, and after accounting for the possibility that AD completion rates may  
1603 differ among the three arms by using the randomization arm as the IV. Thus, the estimated effect of the  
1604 choices patients make is adjusted for the percentage of assigned patients who complete an AD at all,  
1605 and the percentage who opt out from their assigned default option. This IV uses data on all randomized  
1606 patients and then adjusts for AD completion rates, thereby attenuating the selection effects.

1607 This analysis also requires the use of principal stratification methods to formulate the causal quantities  
1608 of interest and determine the proportions of patients in each arm who would choose comfort care if  
1609 they were assigned to complete each version of the AD. The analysis assumes that all patients who  
1610 would choose comfort care in a standard AD would also choose it in an AD that defaults to comfort care,  
1611 and that all patients who would choose comfort care in an AD that defaults to aggressive care would  
1612 also choose it in a standard AD or an AD the defaults to comfort care. Coupled with the possibilities that  
1613 some participants would never return an AD, and that others would return an AD but not choose  
1614 comfort care regardless of group assignment, this creates five compliance classes (principal strata) of  
1615 participants. These classes are:

- 1616 I. Patients would not complete an AD regardless of group assignment
- 1617 II. Patients would complete an AD but not choose comfort care regardless of group assignment
- 1618 III. Patients would complete an AD and only choose comfort care if assigned to the comfort-  
1619 default AD
- 1620 IV. Patients would complete an AD and choose comfort care if assigned to the comfort-default  
1621 AD or standard AD
- 1622 V. Patients would complete an AD and choose comfort care regardless of group assignment

1623 Each patient has three potential outcomes (see below). Only one of the potential outcomes can be  
1624 observed, the outcome corresponding to the actual intervention the patient received. This is  
1625 represented by a binary endpoint – whether or not patients would have a high quality of life in the  
1626 future:

1627  $Y_i^A$  = whether patient  $i$  would have high quality of life if assigned to complete an aggressive-default AD  
1628  $Y_i^S$  = whether patient  $i$  would have high quality of life if assigned to complete a standard AD

1629  $Y_i^C$  = whether patient  $i$  would have high quality of life if assigned to complete a comfort-default AD

1630 Our approach assumes the exclusion restriction that AD assignment only influences the potential  
1631 outcomes through the causal pathway of determining which type of care the patient chooses through  
1632 the AD. However, this assumption is likely to hold in this case, because the randomly assigned IV – which  
1633 of three versions of the AD is offered – would not influence outcomes unless it modified the probability  
1634 of AD completion or the choices made in the ADs.

### 1635 **5.3 Secondary analyses**

1636 Secondary outcomes analyses: Secondary outcomes will be analyzed using logistic, linear, or quantile  
1637 regression, as appropriate. The number of hospital and ICU admissions will be analyzed as count data.  
1638 Charges will be inflated to the date on which analyses are performed using the US gross domestic  
1639 product deflator.

1640 In all models, center will be entered as a random effect to adjust for potential clustering within centers  
1641 and to mitigate confounding by clinic. Since center and diagnosis are strongly correlated as we  
1642 mentioned above, we will only include diagnosis as fixed effect in the models. Gender, race (categorical)  
1643 and age (continuous) will be included in all multivariable models based on pre-specified hypotheses, and  
1644 others will be added if their inclusion – singly or jointly – modifies the coefficient for the randomized  
1645 exposure by  $\geq 15\%$ .

### 1646 **5.4 Sensitivity analyses modifying the HFD calculation**

1647 (1) We will impute the HFD for the patients with invalid SSNs. The imputation method will be model  
1648 based multiple imputation approach and we will report the pooled estimates.

1649

## 1650 **6. Sample Size and Power**

1651 We calculate our sample size as that required to rule out a significant reduction in HFDs attributable to  
1652 random assignment to a default AD. This approach entails non-inferiority tests of data from a Poisson  
1653 distribution, such that we seek to reject the hypothesis of a rate ratio (RR) for HFDs that is significantly  
1654  $>1.0$ . By enrolling 270 patients who complete ADs—90 in each of the three arms—we will obtain at least  
1655 80% power to demonstrate non-inferiority up to a margin of an RR for HFDs  $\geq 1.18$  associated with use of  
1656 a default AD. This calculation is based on: (1) a one-sided  $\alpha$  of 0.05, yielding an upper confidence limit on  
1657 the observed RR that falls entirely below an RR of 1.18; (2) a mean number of HFDs in the control group  
1658 of 100, such that a RR of 1.18 would correspond to 15 (15%) fewer HFDs in a given AD group  
1659 ( $100/85=1.18$ ); (3) an allowance for considerable dispersion in the distribution of HFDs; (4) no loss to  
1660 follow-up because all deaths and hospitalizations will be checked against the Social Security Death Index  
1661 and Pennsylvania Health Care Cost Containment Council (PHC4), respectively; (5) an allowance for two  
1662 primary hypotheses tests (comparing both the comfort-default and life-extension default arms to the  
1663 control arm) and (6) a true RR of 1.0. This final choice reflects our hypothesis that assignment to all  
1664 three ADs will produce equivalent numbers of HFDs. If the true RR is below 1.0 (eg, the comfort default  
1665 increases HFDs), power would increase considerably. Further, because simulations used to generate  
1666 these sample size estimates included scenarios with extreme assumptions of data dispersion, and the



1667 proposed sample sizes incorporate this conservative assumption, our observed power is likely to be  
1668 higher than stated.

## 1669 VI. Summary of Changes to the Statistical Analytic Plan

1670

- 1671 1. We redefined the mITT sample to now include who died within 30 days of randomization. This  
1672 change was recommended by our DSMB during our July 19, 2016 meeting, well before any trial  
1673 data were reviewed even in cumulative form, let alone unblinded. Thus, the only exclusion  
1674 criteria were (1) post-randomization ineligible and (2) patients who withdrew.
- 1675 2. We had considerable difficulty obtaining responses from surrogates after patients died. The low  
1676 response rate was discussed with the DSMB at our March 1, 2017 meeting. After reviewing the  
1677 cumulative data (not stratified by arm) on April 20, 2018, we elected to forgo analyses of  
1678 surrogate-reported outcomes.
- 1679 3. We were not able to evaluate hospice utilization because these data were unexpectedly missing  
1680 from the NJ and PA databases. We discussed this with the DSMB at our March 1, 2017 meeting.  
1681 During the Spring of 2018, we pursued other hospice-specific databases and spoke with hospice  
1682 organizations at both participating health systems. However, because patients from both  
1683 participating health systems may end up in multiple different hospice systems, we were  
1684 concerned that this approach would yield incomplete data. Thus, we abandoned the plan to  
1685 analyze hospice utilization on May 25, 2018. This decision was made by the PI (Dr. Halpern), who  
1686 was still blinded to trial data.
- 1687 4. We only analyzed satisfaction with advance care planning at 2 months following AD completion  
1688 because the data available to analyze the 6 and 12 months measures were frequently missing.  
1689 This choice was similarly made by Dr. Halpern while blinded to arm-specific data.
- 1690 5. We elected not to conduct the proposed sensitivity analysis in which the primary outcome was  
1691 changed to "Healthcare facility-free days," which would represent the number of days that a  
1692 patient spent alive and outside an acute care facility, a chronic care facility, or a nursing home.  
1693 We abandoned this plan because we could not obtain reliable data on days spent in the latter  
1694 two types of facilities.

1695 All of the above modifications were made prior to unblinding of trial data to anyone other than the Data  
1696 Manager, Brian Bayes. Mr. Bayes had no role in making the foregoing decisions. Unblinded analyses  
1697 were then prepared by Dr. Chowdhury, in collaboration with Drs. Halpern, Small, and Troxel.

- 1698 6. Because the hospital-free days distribution was observed to be highly left skewed regardless of  
1699 duration of follow-up, we chose not to perform the planned sensitivity analysis using different  
1700 time cut-offs. This decision was made on August 1, 2018, by Drs. Halpern, Chowdhury, and  
1701 Troxel.
- 1702 7. Due to unplanned missing data on the primary outcome measure, we used multiple imputation  
1703 to impute missing HFD data for the 55 patients with invalid SSNs. We elected, on August 8,  
1704 2018, to report these analyses among all patients in the mITT sample using imputation, and  
1705 among the 88.8% of patients with observed outcomes.

- 1706 8. Also on August 8, 2018, we elected to compare patient-level characteristics between the 55  
1707 patients who did not provide valid SSNs and the 437 patients who did provide valid SSNs. We  
1708 made this decision so as to assess the possibility of selection effects stemming from this form of  
1709 non-response in the analyses without imputed data.
- 1710 9. Because both the mITT and CATE analyses were null, we elected not to perform the per-protocol  
1711 analysis as had originally been planned, because inferences from such an analysis would have  
1712 yielded ambiguous conclusions. This choice was made by Drs. Halpern, Chowdhury, Small, and  
1713 Troxel on September 17, 2018.
- 1714 10. Also on September 17, 2018, we elected not to perform the proposed subgroup analyses for  
1715 purposes of this first manuscript due to space considerations, and to instead report these in a  
1716 subsequent brief manuscript.
- 1717 11. We also modified the plans for mediator analyses on September 17, 2018. We elected not to  
1718 examine mediation of the primary outcome by uploading of AD into the EHR because the  
1719 primary comparison of the randomization group on this outcome was null. We elected to pursue  
1720 the second proposed mediator analysis, on the outcome of goal-concordant care, in a  
1721 subsequent report.

1722 The Statistical Analysis Plan was considered final at close of business on September 17, 2018.

- 1723 12. Afterwards, during preparation of our manuscript for submission, we elected to pursue per-  
1724 protocol analyses among the 186 patients who returned ADs, were debriefed, and had their ADs  
1725 uploaded into the EHR. We reasoned that this would assist in interpretation of a trial reporting  
1726 no differences across arms in any clinical outcomes. In reporting this analysis, we clearly specify  
1727 that it was a post-hoc analysis.
- 1728 13. During peer-review of our submitted manuscript, protocol, and SAP, reviewers and editors  
1729 correctly noted an error in Hypothesis 2a in the original SAP, which stated that we hypothesized  
1730 that ADs with comfort-oriented defaults would *increase* the number of hospital-free days. This  
1731 hypothesis was inconsistent with what we stated in our trial protocol (in which we state that  
1732 “we will determine whether this simple and readily scalable intervention can improve patients’  
1733 quality of life and reduce resource utilization *without reducing* the number of days that patients  
1734 are alive and living outside of an acute-care hospital.”) Indeed, this language of testing the  
1735 noninferiority of comfort-oriented defaults on the outcome of hospital-free days is also present  
1736 in our original grant application and our original posting of the trial protocol on ClinicalTrials.gov  
1737 on December 16, 2013. We regret this error in the original SAP, and have corrected it in the  
1738 submitted final SAP such that hypothesis 2a now correctly reads: “Compared with standard ADs,  
1739 neither ADs with preselected comfort care options nor ADs with preselected options intended  
1740 to promote life extension will reduce patients’ hospital-free days (HFDs), a measure that  
1741 represents the number of days alive and not in an acute care facility.”

1742

1743