NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

pair
Palliative and Advanced Illness Research Center

Improving serious illness care through large pragmatic trials *

Scott D. Halpern, MD, PhD

John M. Eisenberg Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy

Director, Palliative and Advanced Illness Research (PAIR) Center

Director, Roybal P30 Center on Palliative Care in Dementia

University of Pennsylvania Perelman School of Medicine

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@ScottHalpernMD

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Musings of a naïve Ph.D. student

Prospective preference assessment:
a method to enhance the ethics and efficiency of randomized controlled trials

Scott D. Halpern, M.S.C.E.

Controlled Clinical Trials 23 (2002) 274–288

The Continuing Unethical Conduct of Underpowered Clinical Trials

Scott D. Halpern, MSCE
Jason H. T. Karlawish, MD
Jesse A. Berlin, ScD

Despite long-standing critiques of the conduct of
als, the practice not only remains widespread, but
ing support. Patients and healthy volunteers cor

JAMA. 2002;288:358-362

Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs

Scott D. Halpern, MSCE, Peter A. Ubel, MD, Jesse A. Berlin, ScD, Raymond R. Townsend, David A. Asch, MD, MBA

J GEN INTERN MED 2002;17:689–695.

Empirical Assessment of Whether Moderate Payments Are Undue or Unjust Inducements for Participation in Clinical Trials

Scott D. Halpern, MD, PhD; Jason H. T. Karlawish, MD; David Casarett, MD, MA; Jesse A. Berlin, ScD; David A. Asch, MD, MBA

Arch Intern Med. 2004;164:801-803

ORIGINAL ARTICLE

Explanatory and Pragmatic Attitudes in Therapeutical Trials

Daniel Schwartz, Joseph Lellouch

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

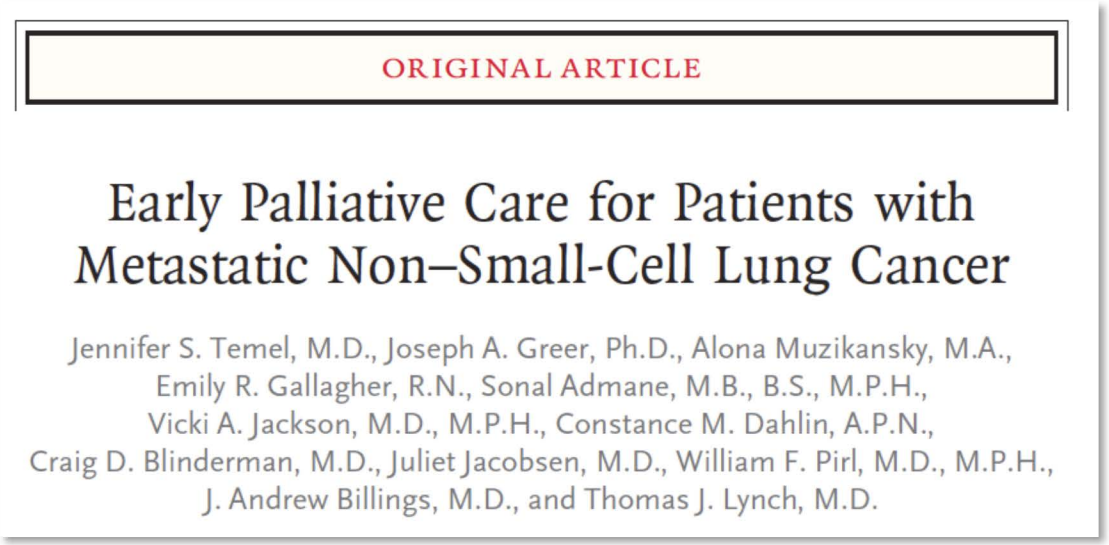
The "comparison between two treatments" is a problem which is inadequately specified even in its over-all characteristics. It may imply one of at least two types of problem which are basically different.

The first type corresponds to an explanatory approach, aimed at *understanding*. It seeks to discover whether a difference exists between two treatments which are specified by strict and usually simple definitions. Their effects are assessed by bio-

The second type corresponds to a pragmatic approach, aimed at *decision*. It seeks to answer the question—which of the two treatments should we prefer? The definition of the treatments is flexible and usually complex; it takes account of auxiliary

J Chronic Disease 1967 "

Explanatory trials in serious illness care [1]



ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

151 patients randomized (of 283 approached; 53%) in 37 months (4.1 1 patients / month); roughly $2,500 / 1 patient

132 patients randomized (of 313 approached; 1 42%) in 21 months (6.3 patients/month) at cost of $1,515 / patient 1

By Scott D. Halpern, George Loewenstein, Kevin G. Volpp, Elizabeth Cooney, Kelly Vranas, Caroline M. Quill, Mary S. McKenzie, Michael O. Harhay, Nicole B. Gabler, Tatiana Silva, Robert Arnold, Derek C. Angus, and Cindy Bryce

DOI: 10.1377/hlthaff.2012.0895
HEALTH AFFAIRS 32,
NO. 2 (2013): –

THE CARE SPAN

Default Options In Advance Directives Influence How Patients Set Goals For End-Of-Life Care

ORIGINAL ARTICLE

A Randomized Trial of Nighttime Physician Staffing in an Intensive Care Unit

Meeta Prasad Kerlin, M.D., M.S.C.E., Dylan S. Small, Ph.D., Elizabeth Cooney, M.P.H., Barry D. Fuchs, M.D., Lisa M. Bellini, M.D., Mark E. Mikkelsen, M.D., M.S.C.E., William D. Schweickert, M.D., Rita N. Bakhru, M.D., Nicole B. Gabler, Ph.D., M.H.A., Michael O. Harhay, M.P.H., John Hansen-Flaschen, M.D., and Scott D. Halpern, M.D., Ph.D.

1,598 patients (**100%** of those eligible) randomized in 12 months 1

133 patients / month 1

Budget: $80,000 1

$50 / patient 1

N ENGL J MED 368;23 NEJM.ORG JUNE 6, 2013

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SPECIAL ARTICLE

A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation

Scott D. Halpern, M.D., Ph.D., Michael O. Harhay, Ph.D., Kathryn Saulsgiver, Ph.D., Christine Brophy, Andrea B. Troxel, Sc.D., and Kevin G. Volpp, M.D., Ph.D.

6,006 people (**98%** of those eligible*) randomized in 13 months 1

462 people / month 1

Budget: $300,000 1

$50 / patient 1

N Engl J Med 2018;378:2302-10.

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6131 Known smokers were informed of the trial

2% opted out

125 Declined to participate

6006 Were enrolled and underwent randomization
1191 (19.8%) Logged on to the trial website over course of the program (were "engaged")

813 Were assigned to the usual care group
129 (15.9%) Were engaged

1588 Were assigned to the free cessation aids group
277 (17.4%) Were engaged

1199 Were assigned to the free e-cigarettes group
253 (21.1%) Were engaged

1198 Were assigned to the reward incentives plus free cessation aids group
255 (21.3%) Were engaged

1208 Were assigned to the redeemable deposit plus free cessation aids group
277 (22.9%) Were engaged

All employees at 54 U.S. companies who identified as smokers on a health-risk assessment in the 1 prior year were sent 4 emails notifying them of study enrollment 1

Halpern SD, et al. NEJM 2018

8 contrasts specified *a priori*, with significance thresholds adjusted using Holm method

Statistically significant

Not statistically significant

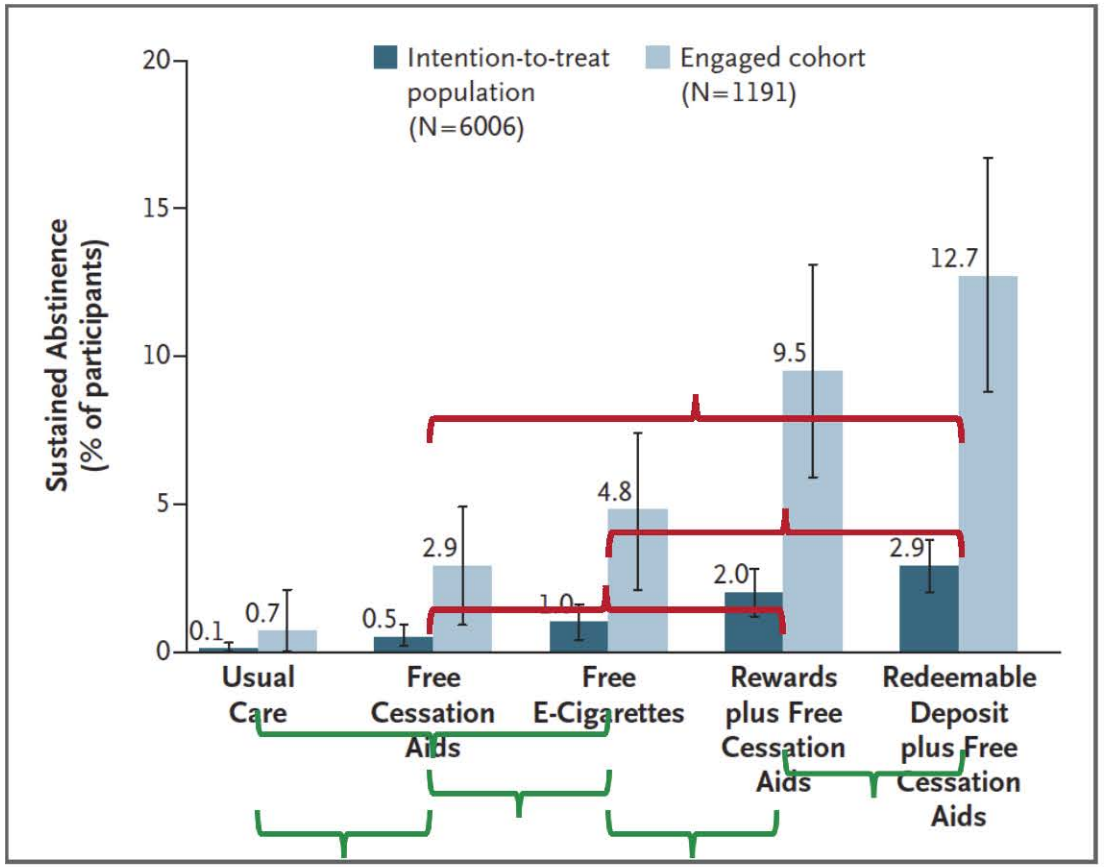

Figure 2. Sustained Smoking Abstinence at 6 Months after the Target Quit Date.

Halpern SD, et al. NEJM 2018 (

Comparing effective smoking cessation interventions among older, underserved patients undergoing lung cancer screening *

Healthy Lungs

pcori Patient-Centered Outcomes Research Institute

Joanna Hart, MD, MS %

Project Details

Principal Investigator	**Project Status**
Scott Halpern, MD, PhD	In progress; Not yet recruiting
Board Approval Date	**Project End Date**
November 2018	March 2025
Organization	**Year Awarded**
University of Pennsylvania	2018
State	**Project Type**
Pennsylvania	Research Project
Funding Announcement	**Project Budget**
Pragmatic Clinical Studies to Evaluate Patient-Centered Outcomes	$11,050,783

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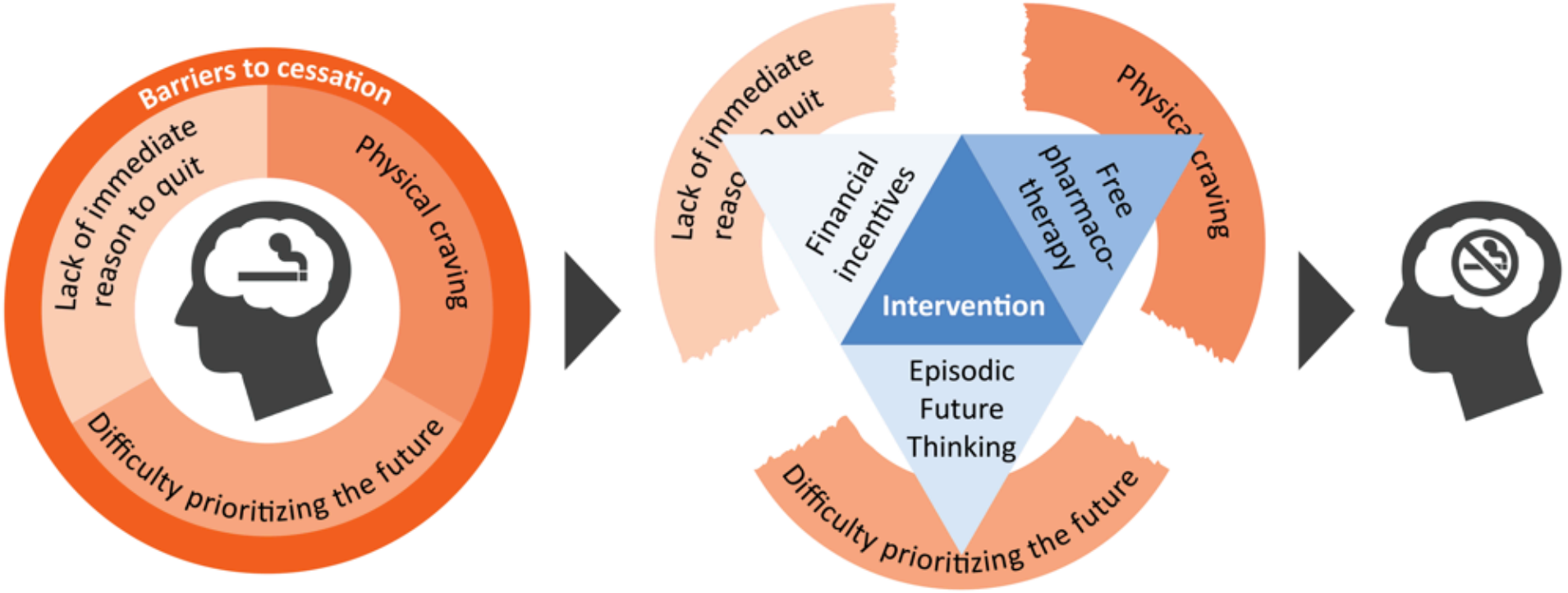
Figure 1: Conceptul model of barriers to smoking cessation that will be addressed by interventions in this RCT



Penn Medicine
The University of Pennsylvania Health System

Henry Ford Health System

KAISER PERMANENTE

Geisinger

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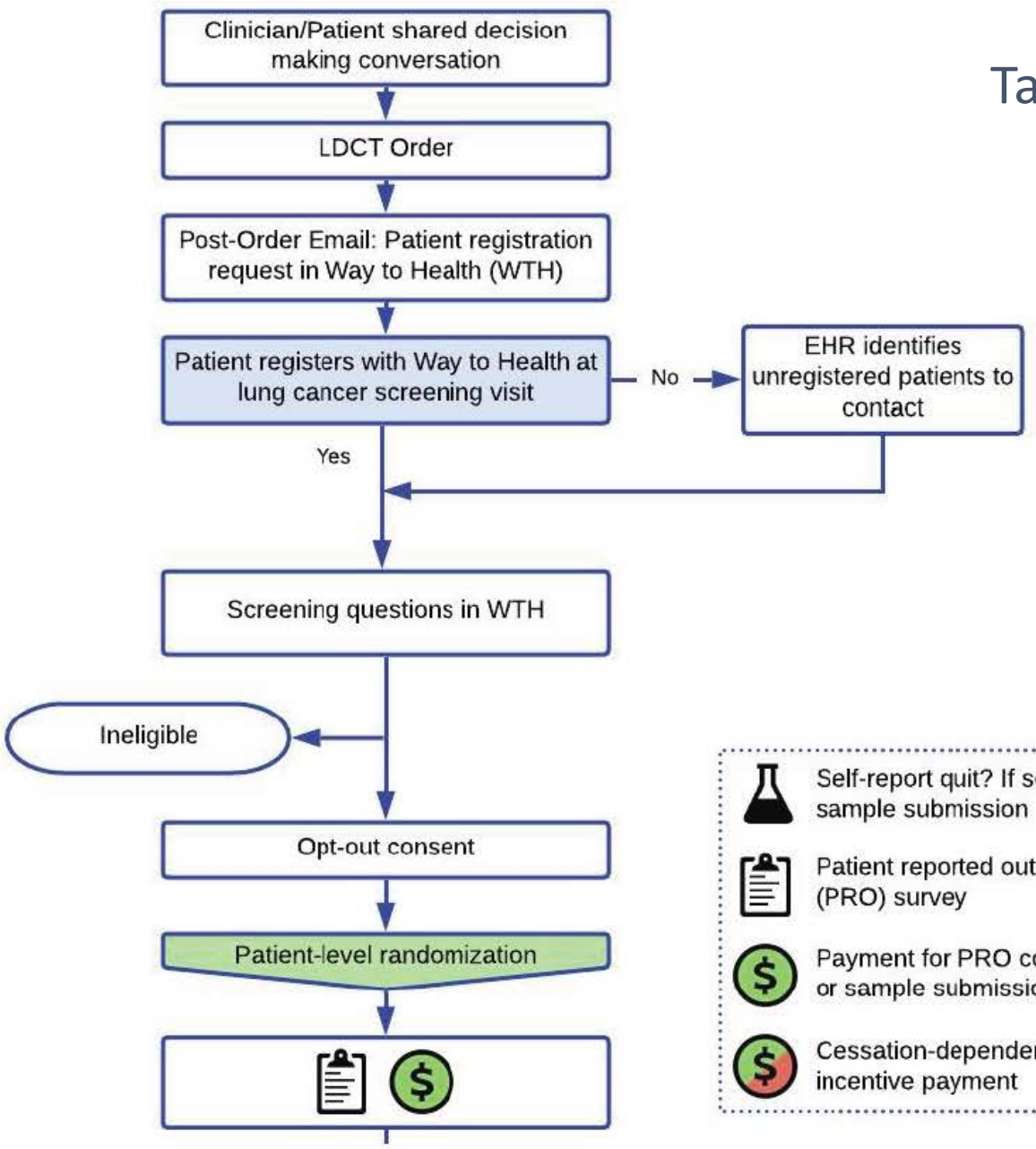
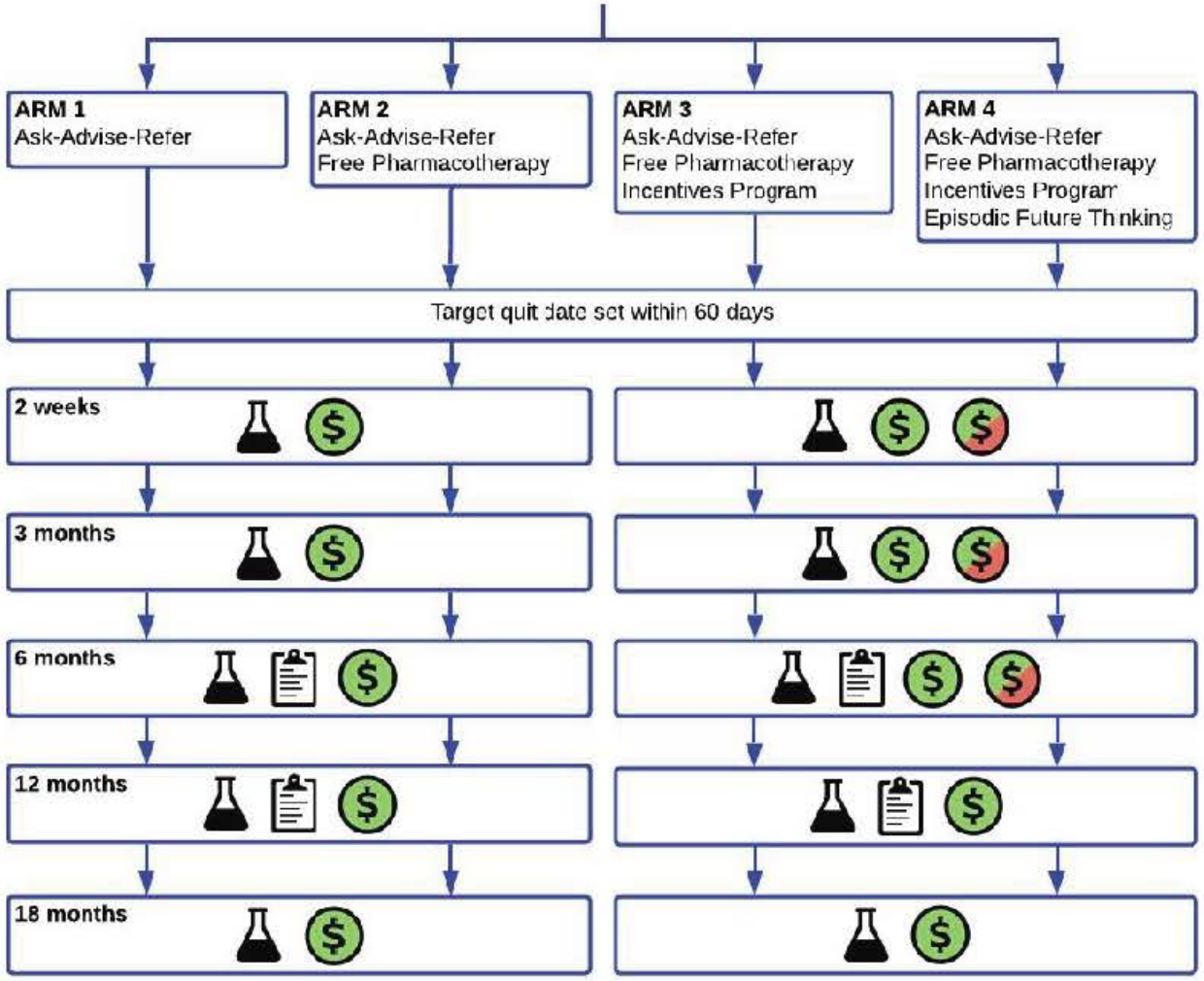
Target sample size: 3,200 underserved smokers undergoing lung cancer screening





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Alterations of informed consent in pragmatic trials +

RESEARCH Open Access

Willingness to participate in pragmatic dialysis trials: the importance of physician decisional autonomy and consent approach

Katherine R. Courtright[1,2], Scott D. Halpern[1,2,3,4], Steven Joffe[2,3,4,5], Susan S. Ellenberg[3,4], Jason Karlawish[4,6], Vanessa Madden[3], Nicole B. Gabler[3], Stephanie Szymanski[3], Kuldeep N. Yadav[3] and Laura M. Dember[3,7*]

Trials (2017) 18:474

Annals of Internal Medicine IDEAS AND OPINIONS

Waivers and Alterations of Research Informed Consent During the COVID-19 Pandemic

Emily A. Largent, JD, PhD, RN; Scott D. Halpern, MD, PhD; and Holly Fernandez Lynch, JD, MBE

This article was published at Annals.org on 15 December 2020.

Pragmatic trials to improve palliative care for hospitalized patients [1]

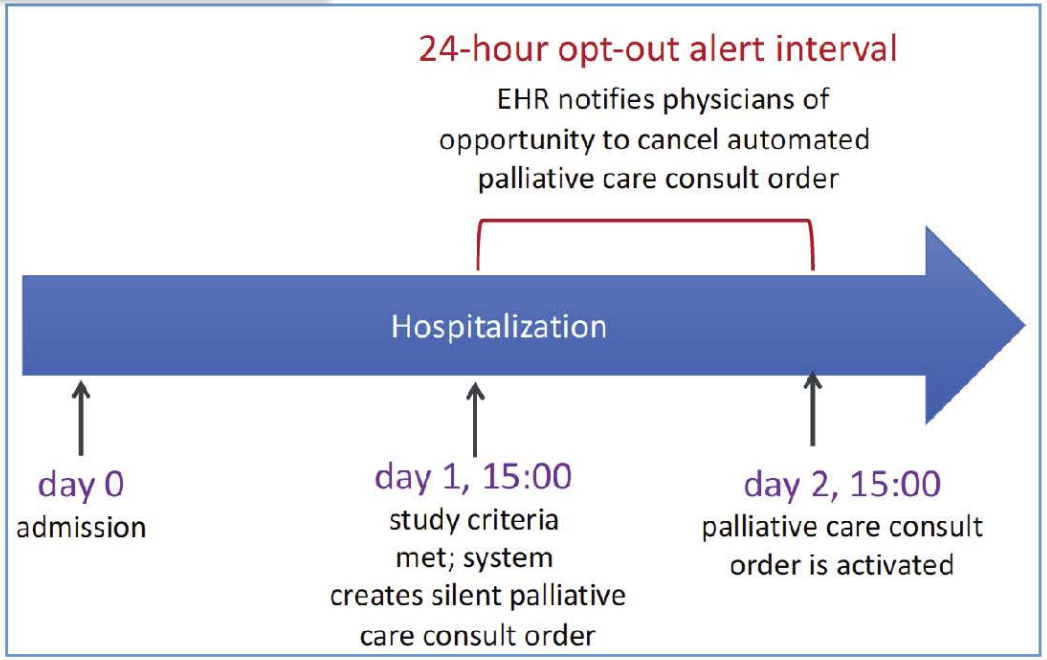
Rationale and Design of the Randomized Evaluation of Default Access to Palliative Services (REDAPS) Trial

Katherine R. Courtright[1,2,3], Vanessa Madden[2,3,4], Nicole B. Gabler[2,3,4], Elizabeth Cooney[2,3,4], Dylan S. Small[4,5], Andrea Troxel[2,4], David Casarett[6,7], Mary Ersek[8,9], J. Brian Cassel[10], Lauren Hersch Nicholas[11], Gabriel Escobar[12], Sarah H. Hill[13], Dan O'Brien[13], Mark Vogel[13,14], and Scott D. Halpern[1,2,3,4,6]

ASCENSION

Comparison: palliative care consultation at MD discretion (usual care) vs. EHR-ordered palliative care consultation on 3rd hospital day (MD can opt out)

Design: Stepped-wedge RCT among patients admitted to 11 Ascension Health hospitals with integrated EHR



Eligibility criteria

Life-limiting illness	*Additional criteria required*
End-stage renal disease (ESRD)	• None
Chronic obstructive pulmonary disease (COPD)	• Home oxygen dependence; *or* • 2 or more additional hospitalizations within 12 months
Dementia (all types)	• Admitted from a long-term-care facility (e.g., nursing home); *or* • Prior placement of surgical feeding tube (e.g., PEG); *or* • 2 or more additional hospitalizations within 12 months

Primary outcome: hospital LOS

Secondary outcomes: use of life support; mortality; readmissions; costs

Courtright KR, et al. Ann Amer Thoracic Soc 2016; 13:1629-39

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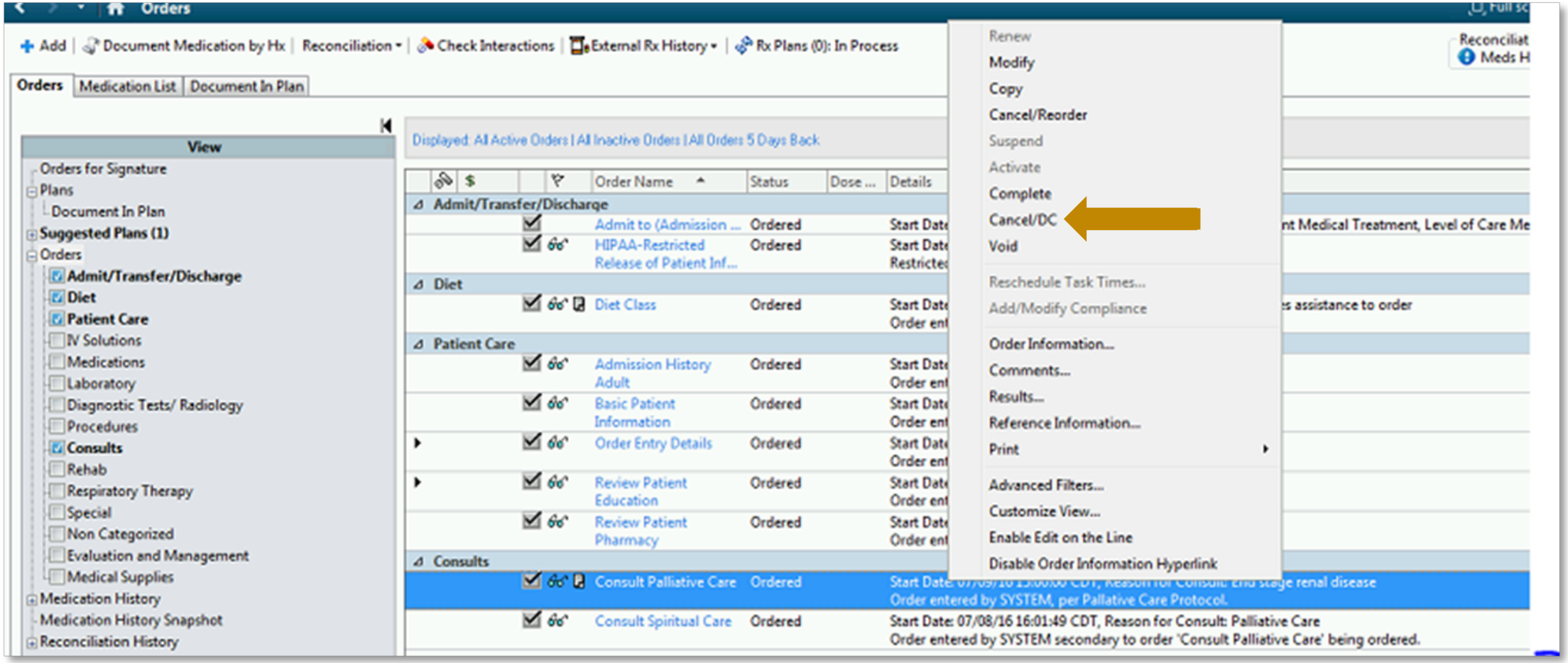
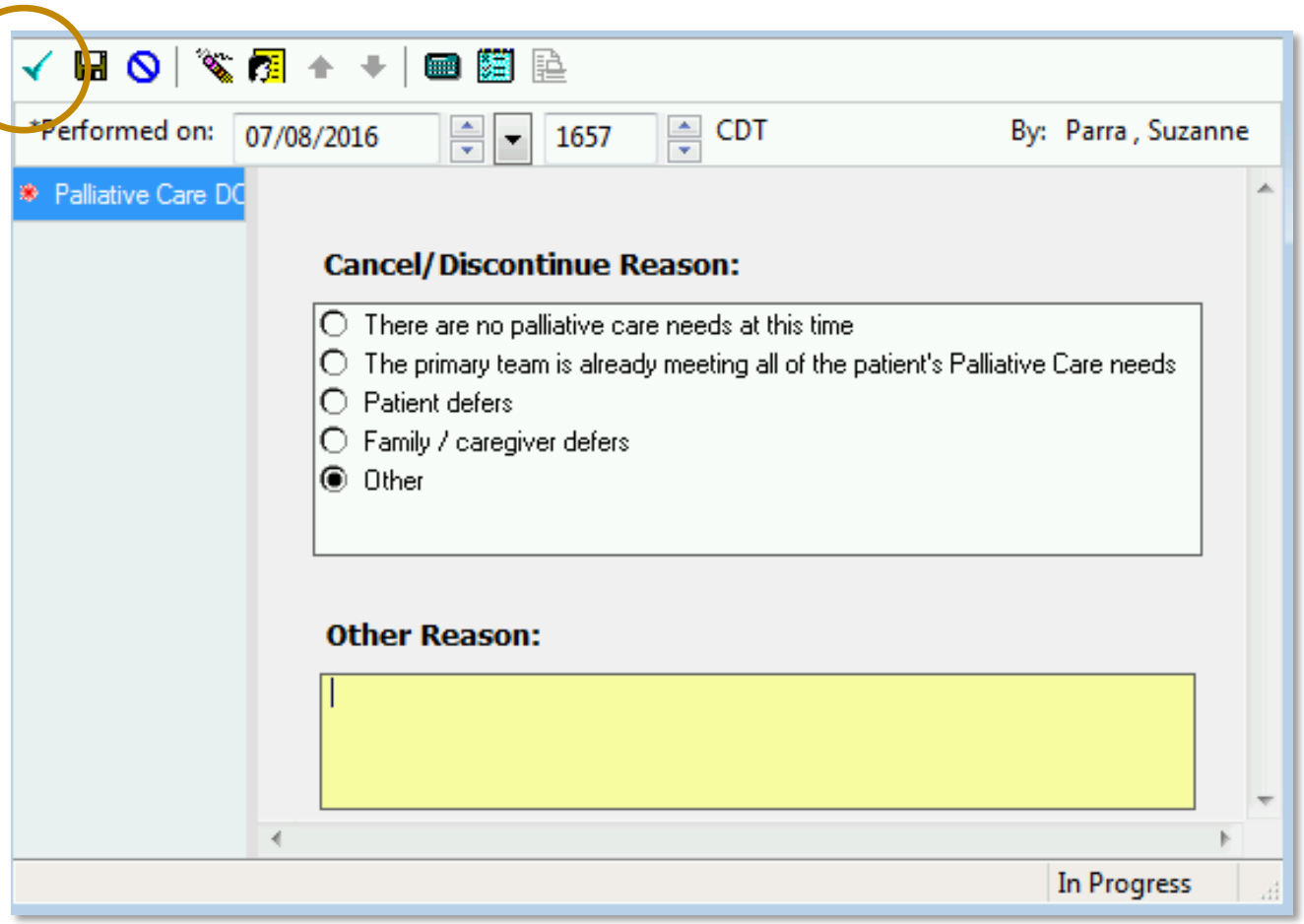
Cancelling the default order



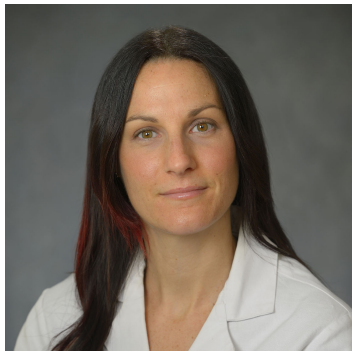
Right-click “Consult Palliative Care” Order and select Cancel/DC *

Must provide reason to cancel order

- Select one reason or enter free text in “Other Reason”
- Click on green check mark to SIGN



Efficiency of REDAPS accrual



Kate Courtright, MD, MS %

- Patients accrued from 3/1/16 - 11/15/18 (32.5 months)
- ITT sample: 34,239 enrolled (1,054 patients / month)
- Modified ITT sample: 24,065 (740 patients / month)
- **$61 (direct costs) / ITT patient** $

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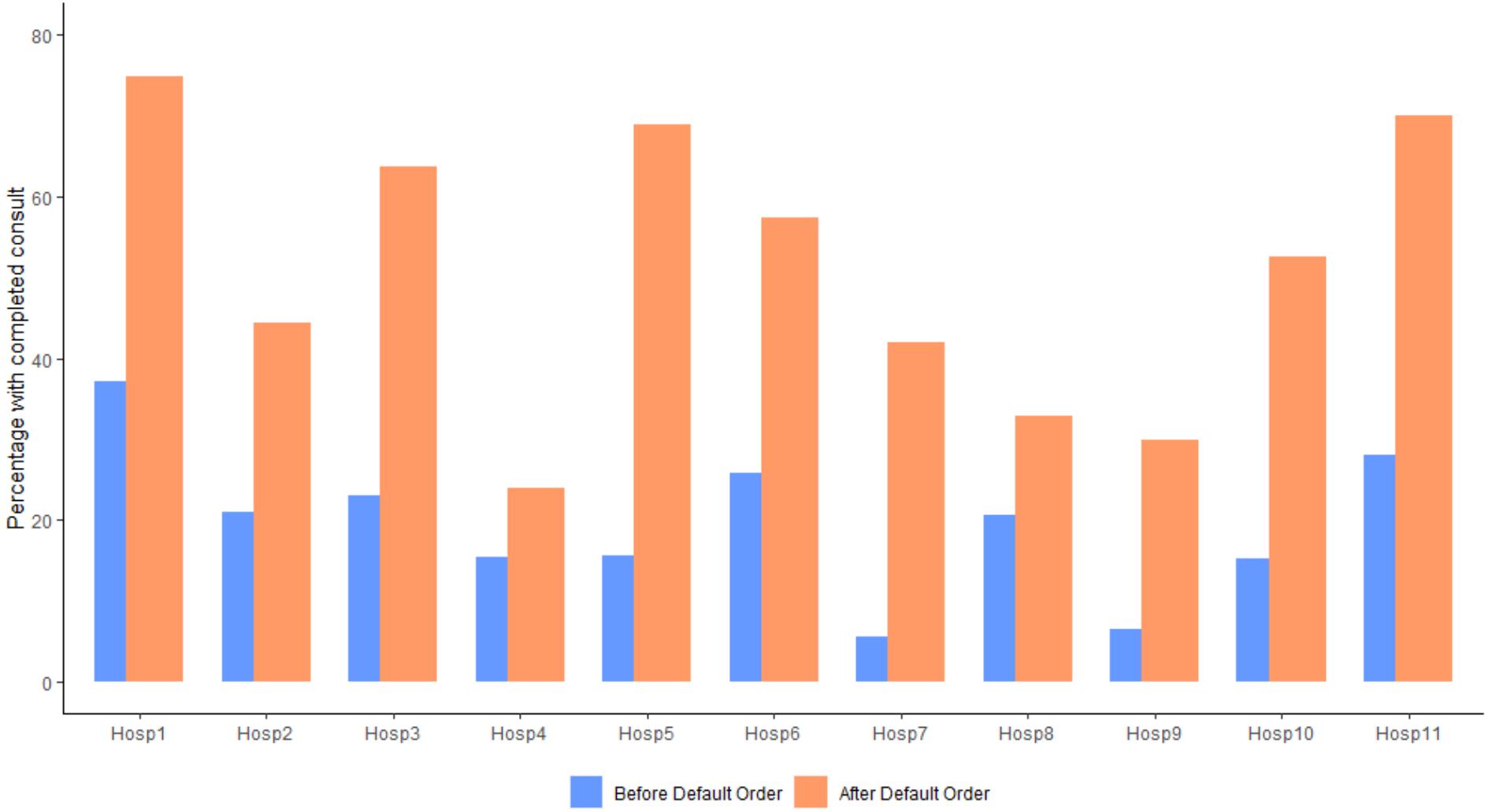
PC consults increased 2.7-fold

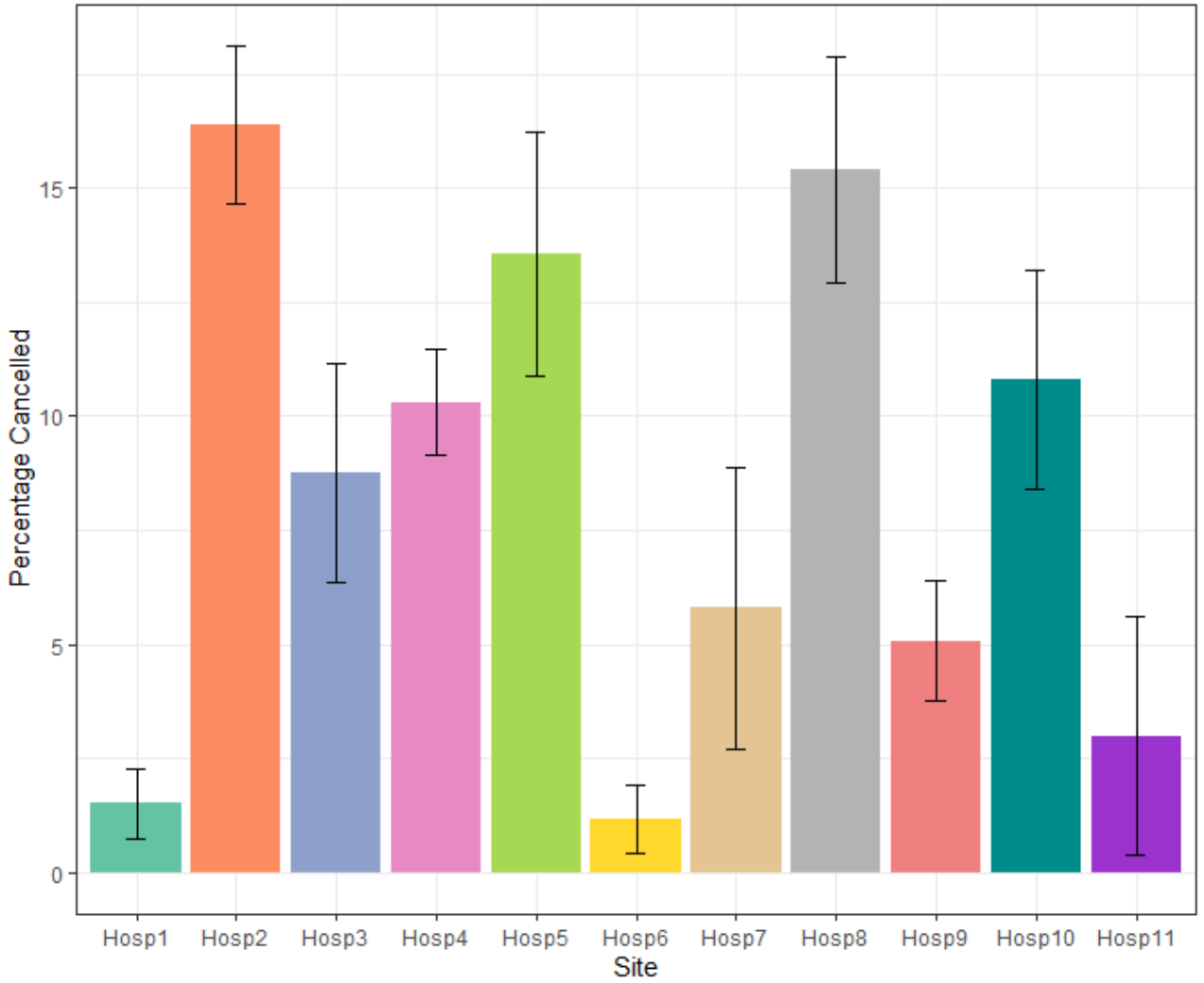


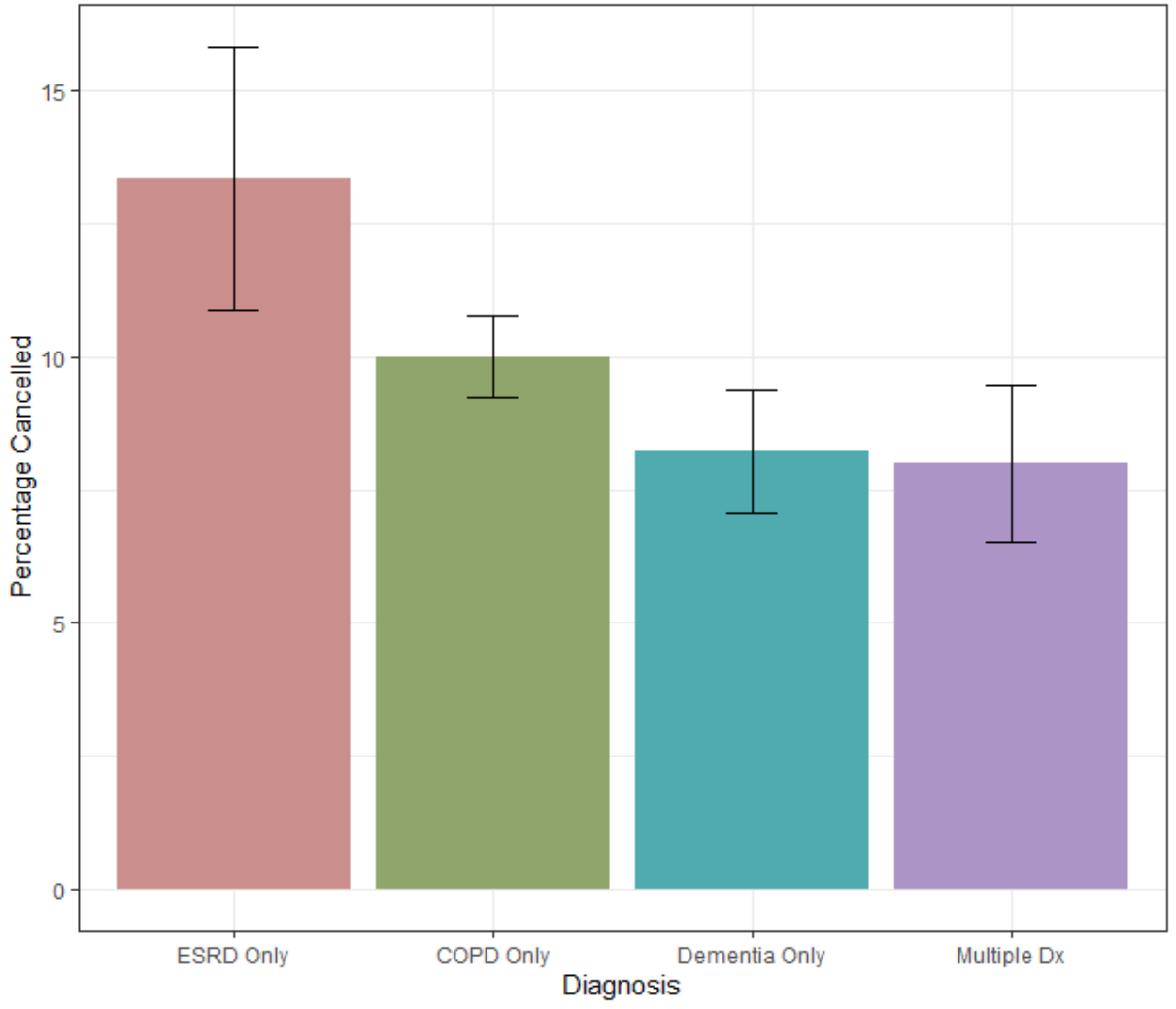
Overall [1]

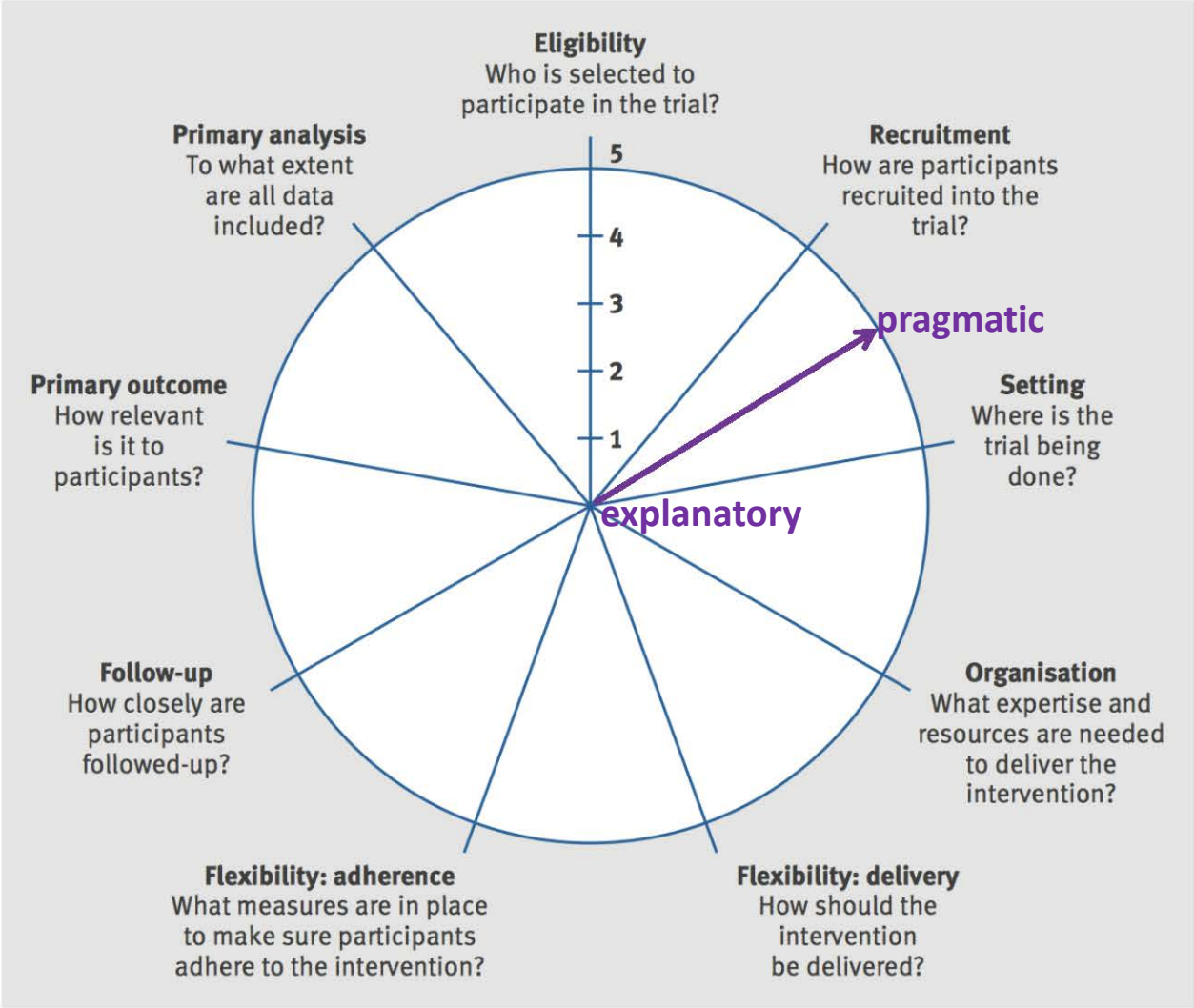
Control: 16.6%

Intervention: 43.9% [3]

Cancellation rates vary by site and diagnosis *

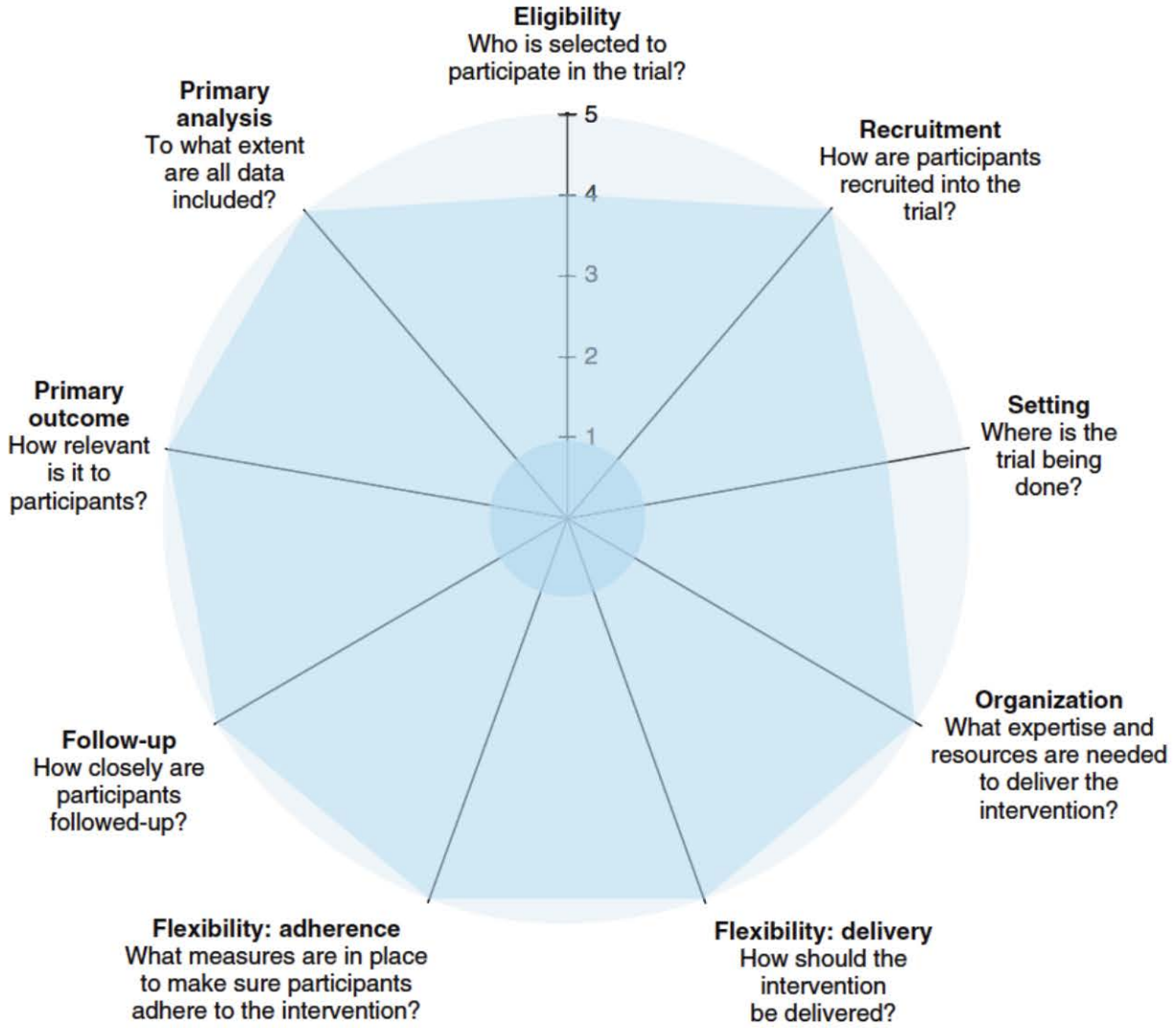






The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.

Louden et al. BMJ. 2015.



Average ratings of REDAPS by trial experts and program officers convened by NIA

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An Official American Thoracic Society/American Association of Critical-Care Nurses/American College of Chest Physicians/Society of Critical Care Medicine Policy Statement: The Choosing Wisely® Top 5 List in Critical Care Medicine

Scott D. Halpern, Deborah Becker, J. Randall Curtis, Robert Fowler, Robert Hyzy, Lewis J. Kaplan, Nishi Rawat, Curtis N. Sessler, Hannah Wunsch, and Jeremy M. Kahn; on behalf of the Choosing Wisely Taskforce

Top 5 List in Critical Care Medicine $

released +
January 11, 2014 @
www.choosingwisely.org +

Choosing Wisely®
An initiative of the ABIM Foundation

Critical Care Societies Collaborative - **Critical Care**

American Association of Critical-Care Nurses · CHEST American College of Chest Physicians · ATS We help the world breathe · Society of Critical Care Medicine

Five Things Physicians and Patients Should Question

1 Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.

Many diagnostic studies (including chest radiographs, arterial blood gases, blood chemistries and counts and electrocardiograms) are ordered at regular intervals (e.g., daily). Compared with a practice of ordering tests only to help answer clinical questions, or when doing so will affect management, the routine ordering of tests increases health care costs, does not benefit patients and may in fact harm them. Potential harms include anemia due to unnecessary phlebotomy, which may necessitate risky and costly transfusion, and the aggressive work-up of incidental and non-pathological results found on routine studies.

2 Don't transfuse red blood cells in hemodynamically stable, non-bleeding ICU patients with a hemoglobin concentration greater than 7 g/dL.

Most red blood cell transfusions in the ICU are for benign anemia rather than acute bleeding that causes hemodynamic compromise. For all patient populations in which it has been studied, transfusing red blood cells at a threshold of 7 g/dL is associated with similar or improved survival, fewer complications and reduced costs compared to higher transfusion triggers. More aggressive transfusion may also limit the availability of a scarce resource. It is possible that different thresholds may be appropriate in patients with acute coronary syndromes, although most observational studies suggest harms of aggressive transfusion even among such patients.

3 Don't use parenteral nutrition in adequately nourished critically ill patients within the first seven days of an ICU stay.

For patients who are adequately nourished prior to ICU admission, parenteral nutrition initiated within the first seven days of an ICU stay has been associated with harm, or at best no benefit, in terms of survival and length of stay in the ICU. Early parenteral nutrition is also associated with unnecessary costs. These findings are true even among patients who cannot tolerate enteral nutrition. Evidence is mixed regarding the effects of early parenteral nutrition on nosocomial infections. For patients who are severely malnourished directly prior to their ICU admission, there may be benefits to earlier parenteral nutrition.

4 Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation.

Many mechanically ventilated ICU patients are deeply sedated as a routine practice despite evidence that using less sedation reduces the duration of mechanical ventilation and ICU and hospital length of stay. Several protocol-based approaches can safely limit deep sedation, including the explicit titration of sedation to the lightest effective level, the preferential administration of analgesic medications prior to initiating anxiolytics and the performance of daily interruptions of sedation in appropriately selected patients receiving continuous sedative infusions. Although combining these approaches may not improve outcomes compared to one approach alone, each has been shown to improve patient outcomes compared with approaches that provide deeper sedation for ventilated patients.

5 Don't continue life support for patients at high risk for death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort.

Patients and their families often value the avoidance of prolonged dependence on life support. However, many of these patients receive aggressive life-sustaining therapies, in part due to clinicians' failures to elicit patients' values and goals, and to provide patient-centered recommendations. Routinely engaging high-risk patients and their surrogate decision makers in discussions about the option of foregoing life-sustaining therapies may promote patients' and families' values, improve the quality of dying and reduce family distress and bereavement. Even among patients pursuing life-sustaining therapy, initiating palliative care simultaneously with ongoing disease-focused therapy may be beneficial.

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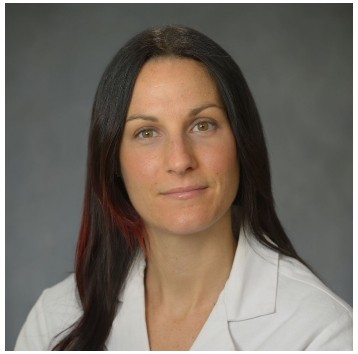
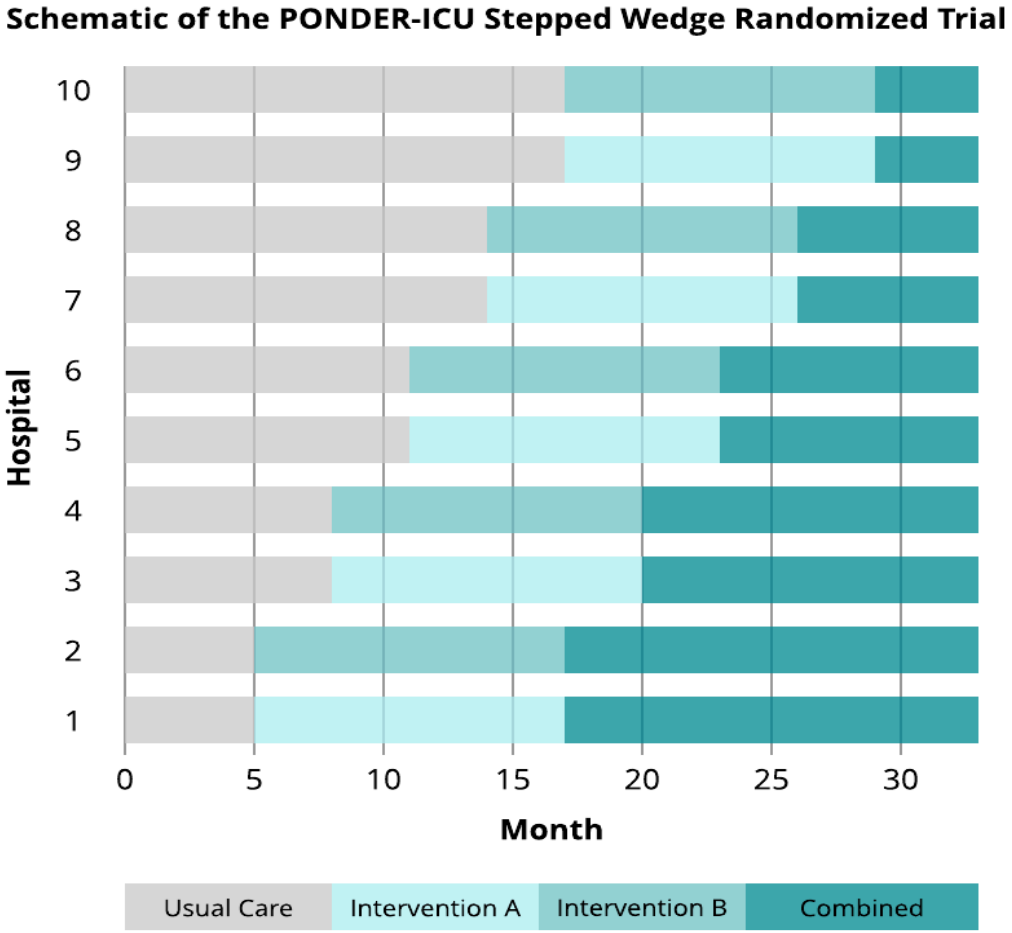
***PONDER-ICU**: Prognosticating Outcomes and Nudging " Decisions with Electronic Records in the ICU "*

- Age ≥ 18
- Mechanical ventilation for ≥ 2 days
- ≥ 1 life-limiting illness present on admission



Atrium Health



Kate Courtright, MD, MS %

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Prognosticating Outcomes and Nudging Decisions with Electronic Records in the Intensive Care Unit Trial Protocol

Katherine R. Courtright[1,2], Erich M. Dress[1], Jaspal Singh[3], Brian A. Bayes[1], Marzana Chowdhury[1], Dylan S. Small[4], Timothy Hetherington[5], Lindsay Plickert[6], Michael E. Detsky[7], Jason N. Doctor[8], Michael O. Harhay[1,2,9*], Henry L. Burke[10], Michael B. Green[3], Toan Huynh[11], D. Matthew Sullivan[6], and Scott D. Halpern[1,2];

Focusing effect: require physicians to predict their patients' functional outcomes 6 months later)

1. Do you think the patient will be alive 6 months from now?

- ○ Yes
- ○ No

2. If yes, what do you think the patient's overall functional status will be 6 months from now?

- ○ Will have no noticeable limitations in physical and/or cognitive function
- ○ Will have mild limitations in physical and/or cognitive function
- ○ Will have moderate limitations in physical and/or cognitive function
- ○ Will have substantial limitations in physical and/or cognitive function
- ○ Will be bedbound and almost entirely dependent on others

Atrium Health

Annals of the American Thoracic Society 2020

Prognosticating Outcomes and Nudging Decisions with Electronic Records in the Intensive Care Unit Trial Protocol

Katherine R. Courtright[1,2], Erich M. Dress[1], Jaspal Singh[3], Brian A. Bayes[1], Marzana Chowdhury[1], Dylan S. Small[4], Timothy Hetherington[5], Lindsay Plickert[6], Michael E. Detsky[7], Jason N. Doctor[8], Michael O. Harhay[1,2,9*], Henry L. Burke[10], Michael B. Green[3], Toan Huynh[11], D. Matthew Sullivan[6], and Scott D. Halpern[1,2];

Focusing effect: require physicians to predict their patients' functional outcomes 6 months later)

Accountable justification: require physicians to offer comfort care or justify why not in EHR

1. Have you offered the patient or his/her surrogate decision maker the option of care focused primarily on comfort during this ICU stay (including withdrawal of life support)?

- ○ Yes
- ○ No

2. If no, please provide a brief justification in the box below. Others will see your response in the medical record. If no justification is entered, the phrase "no justification given" will appear.

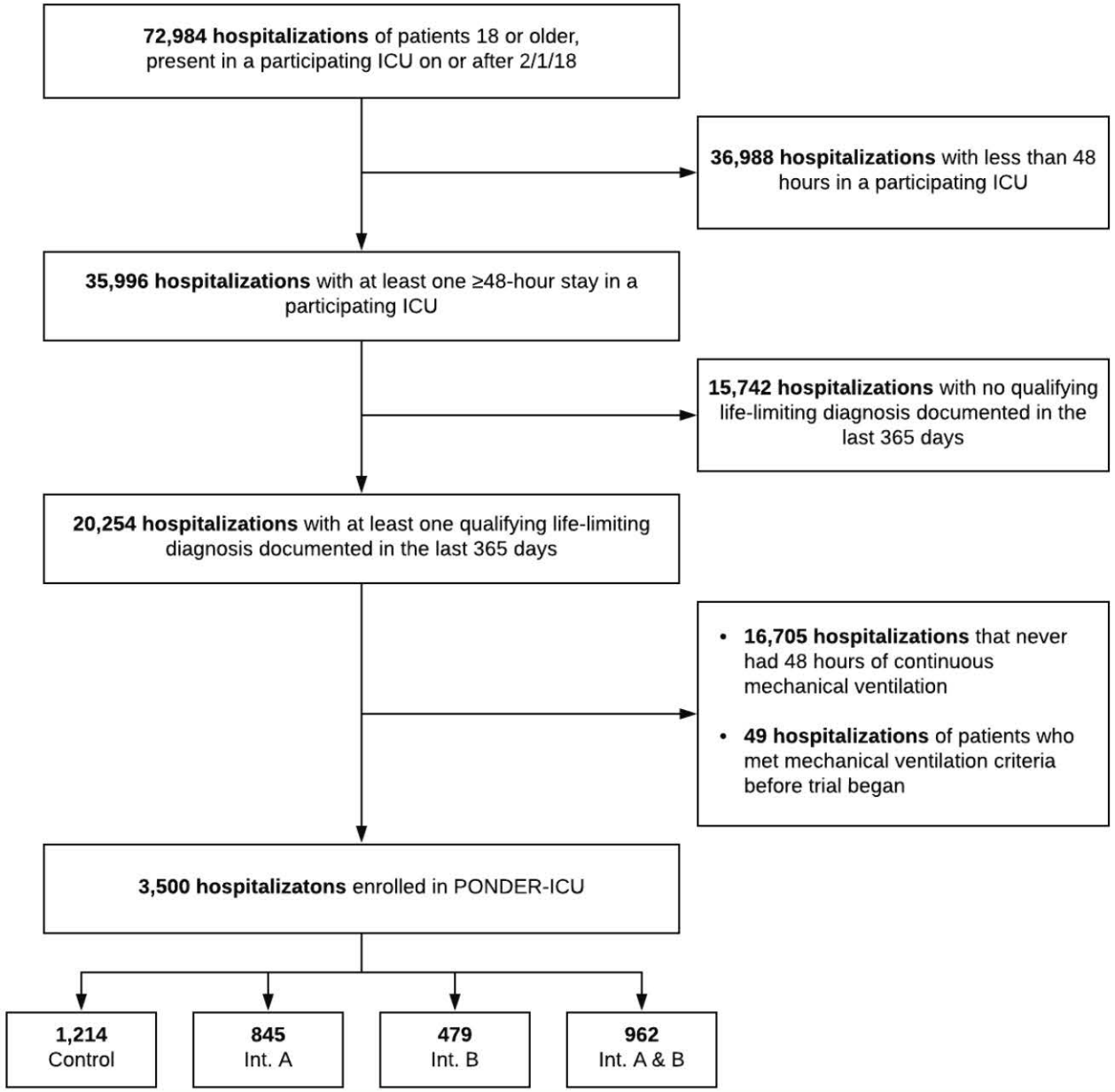
Atrium Health

Annals of the American Thoracic Society 2020

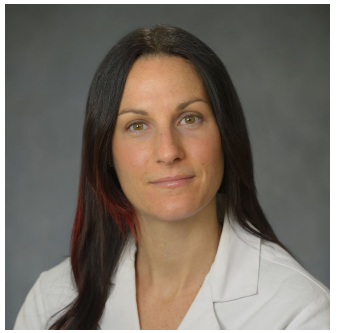
PONDER-ICU

- Accrued 100% of mechanically ventilated patients admitted with life-limiting illnesses from Feb 1, 2018 - Oct 31, 2020.

- Enrolled 3,500 patients - $158 (direct costs) / patient



PONDER – Palliative Care [1]



Kate Courtright, MD, MS

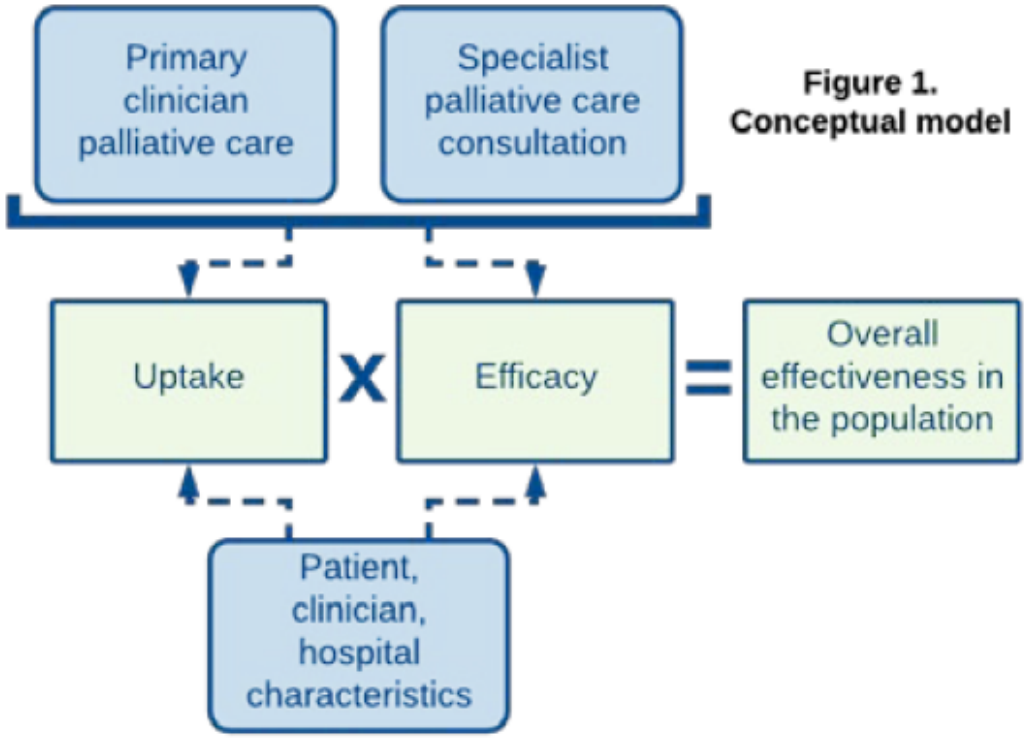
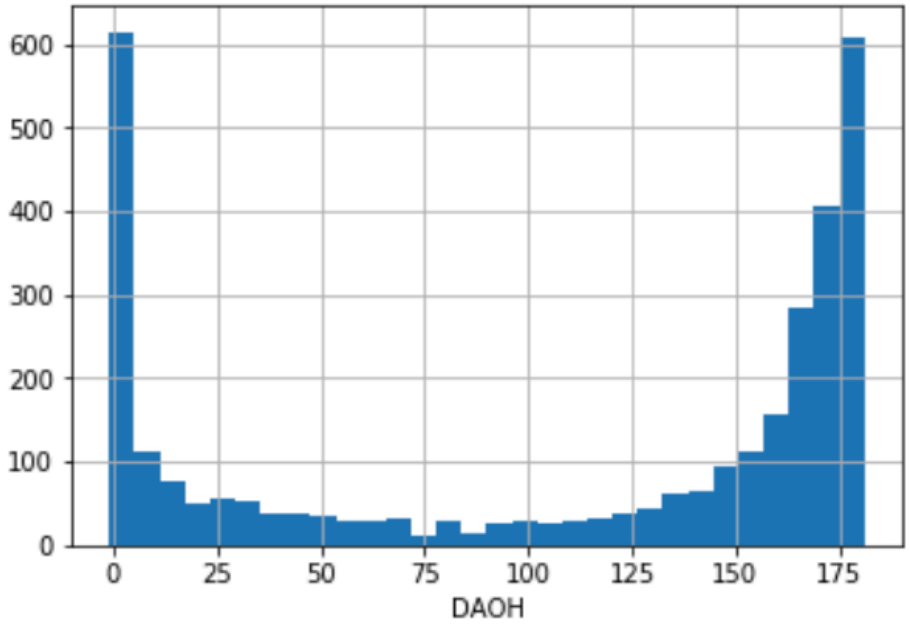
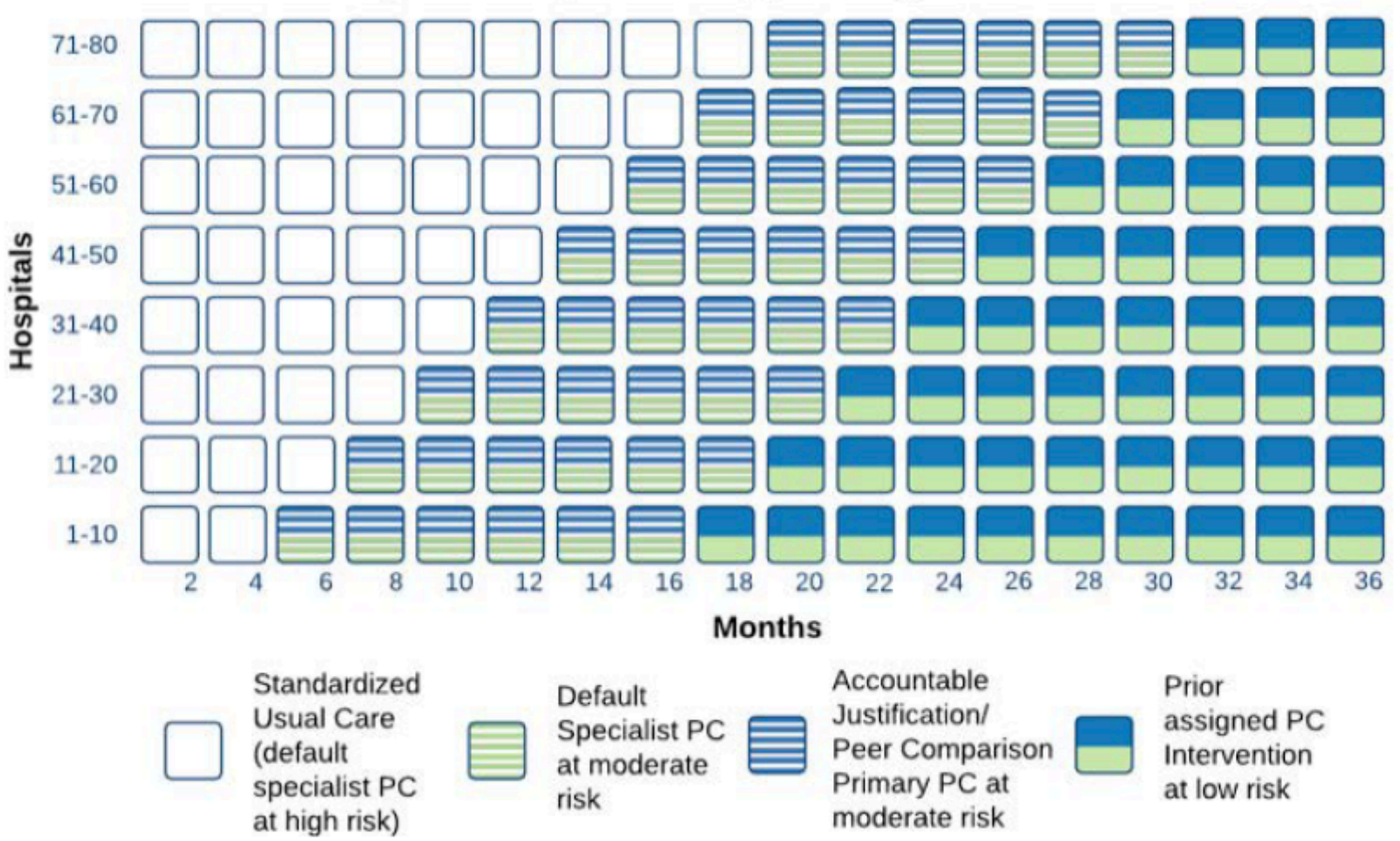


Figure 1. Conceptual model

Primary outcome: Days alive & outside the hospital (DAOH) through 6 months



PONDER – Palliative Care [1]



Atrium Health

(10 hospitals) %

Providence

(33 hospitals) %

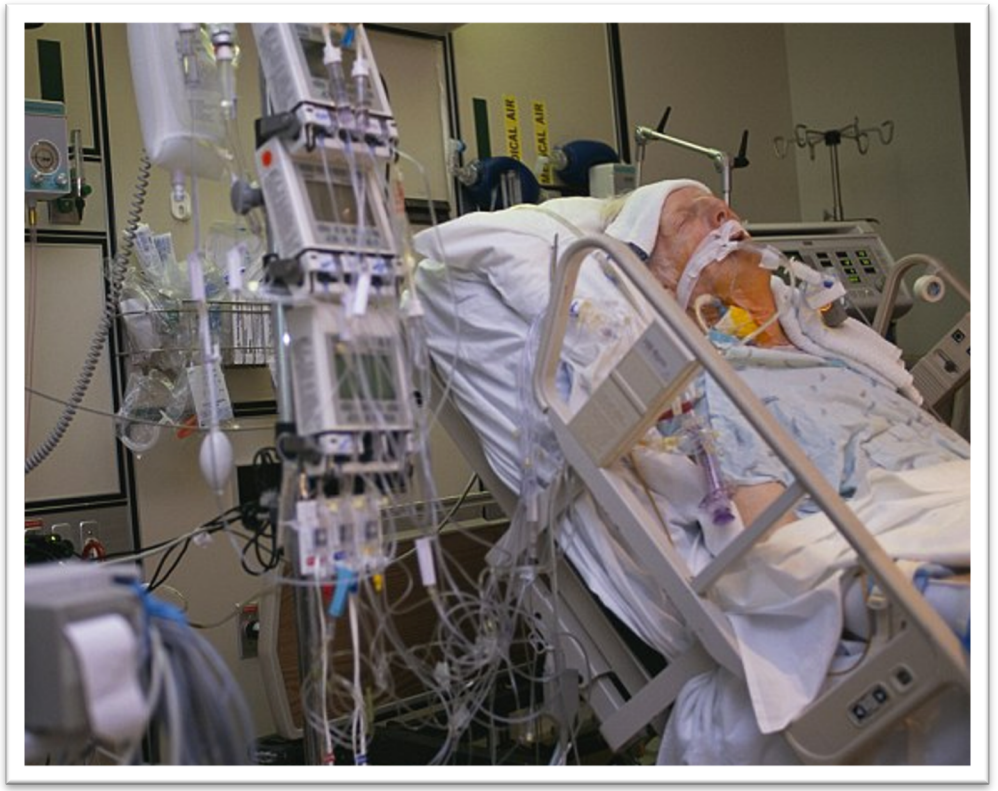
Trinity Health

(37 hospitals)

Pragmatism of the proposed trial on PRECIS-2 criteria*	
Domain	***Relevant trial features***
Eligibility	All hospitalized patients with 6-month risk of death > 40%
Recruitment	Automated via electronic health record, waiver of consent
Setting	80 hospitals in 3 of 10 largest U.S. health systems
Organization	No onsite research staff; clinician training only as part of intervention
Flexibility of delivery	Interventions delivered through usual EHR and clinician communication portals
Flexibility of adherence	Automated, web-based adherence promotion and monitoring
Follow-up	Outcomes data collected through EHRs, links to claims data, and automated, web-based research portal
Primary outcome	Chosen by stakeholders, important to all stakeholders
Primary analysis	Data available for all participants, intention-to-treat analyses

**Criteria from Loudon et al. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015*

Pragmatic trials to improve critical care delivery



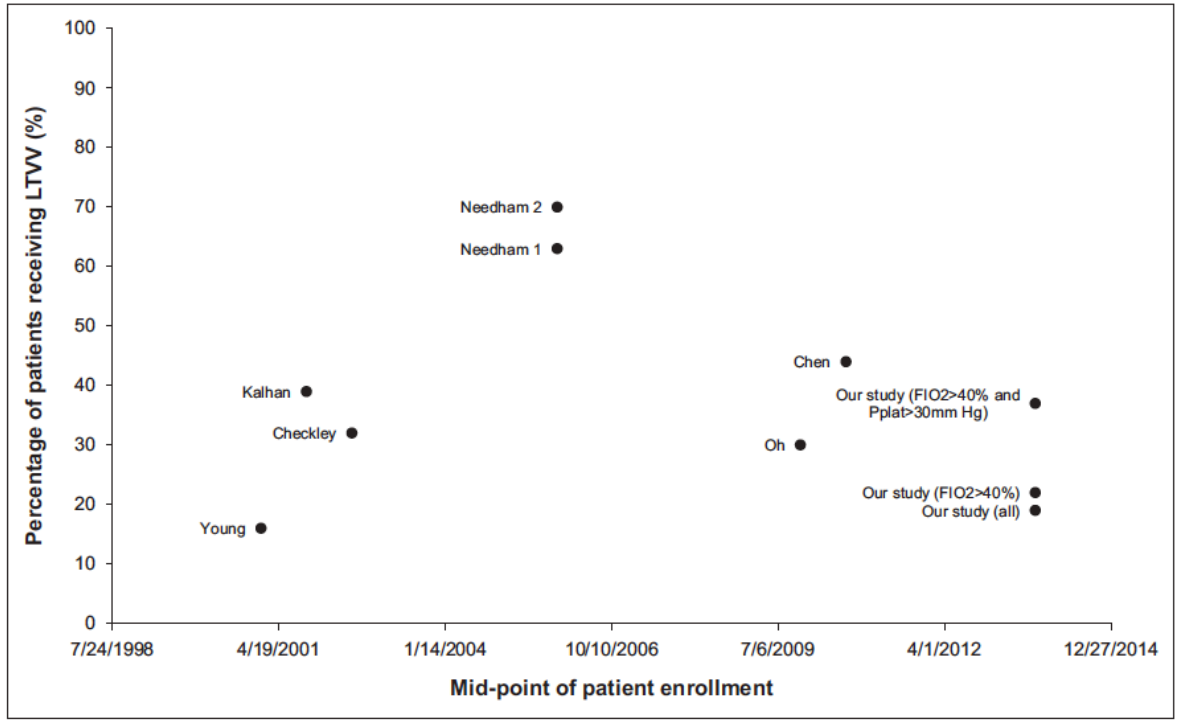
VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

10% absolute mortality reduction

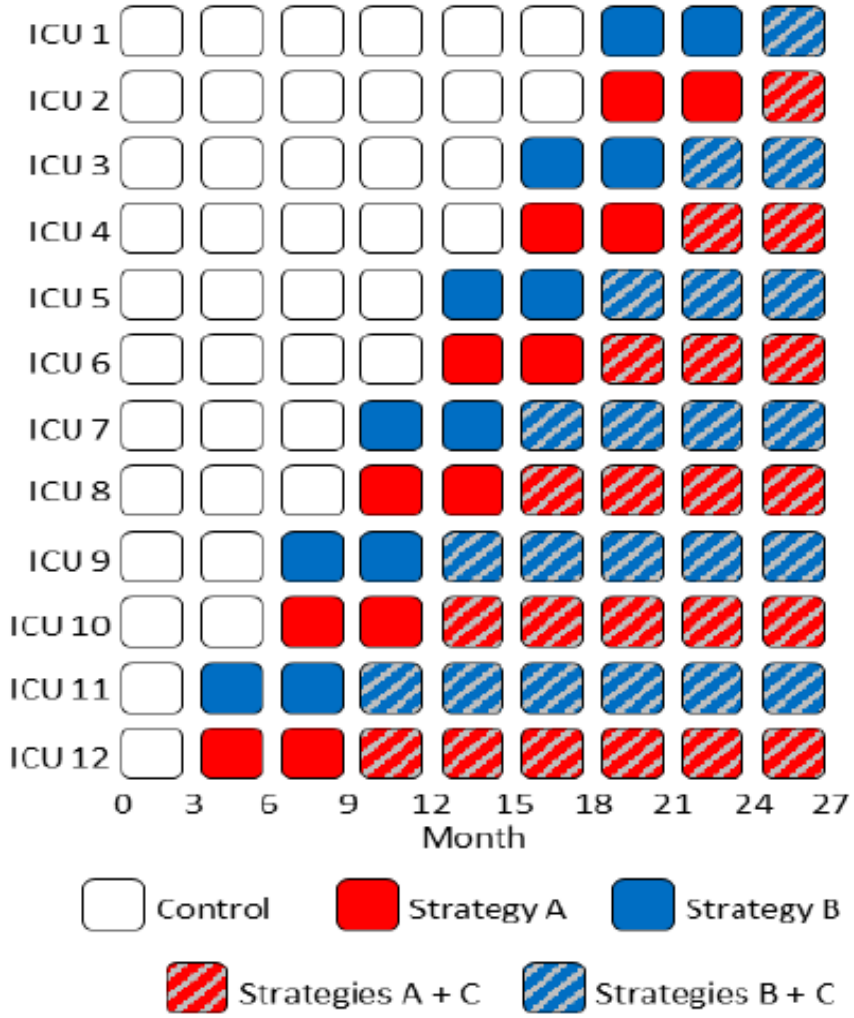
But MAJOR evidence-to-practice gap…



Weiss CH et al. Crit Care Med 2014

Nudging lung-protective ventilation [1]

Meeta Kerlin, MD, MS [2]



- A: Default MV order set *
- B: Physician-directed accountable justification of MV orders
- C: RT-directed accountable justification of MV documentation

R01 HL141608

NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

Penn
University of Pennsylvania

The pair Center

Nudging lung-protective ventilation

- Enrollment to commence April 1 (delayed due to COVID)
- Estimated enrollment: 13,000 patients
- Enrollment duration: 27 months
- Direct costs: $2,055,605

481 mechanically ventilated patients / month *
$158 / patient *

Meeta Kerlin, MD, MS – R01 HL141608

STAND Trial

Study of Therapeutic Exercise in Acute Respiratory Failure to Improve Neuromuscular Disability

MPIs: Halpern, Jablonski, Schweickert $

Sponsor: PAIR Center $

Budget: $80,000 $

NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

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University of Pennsylvania

The pair Center

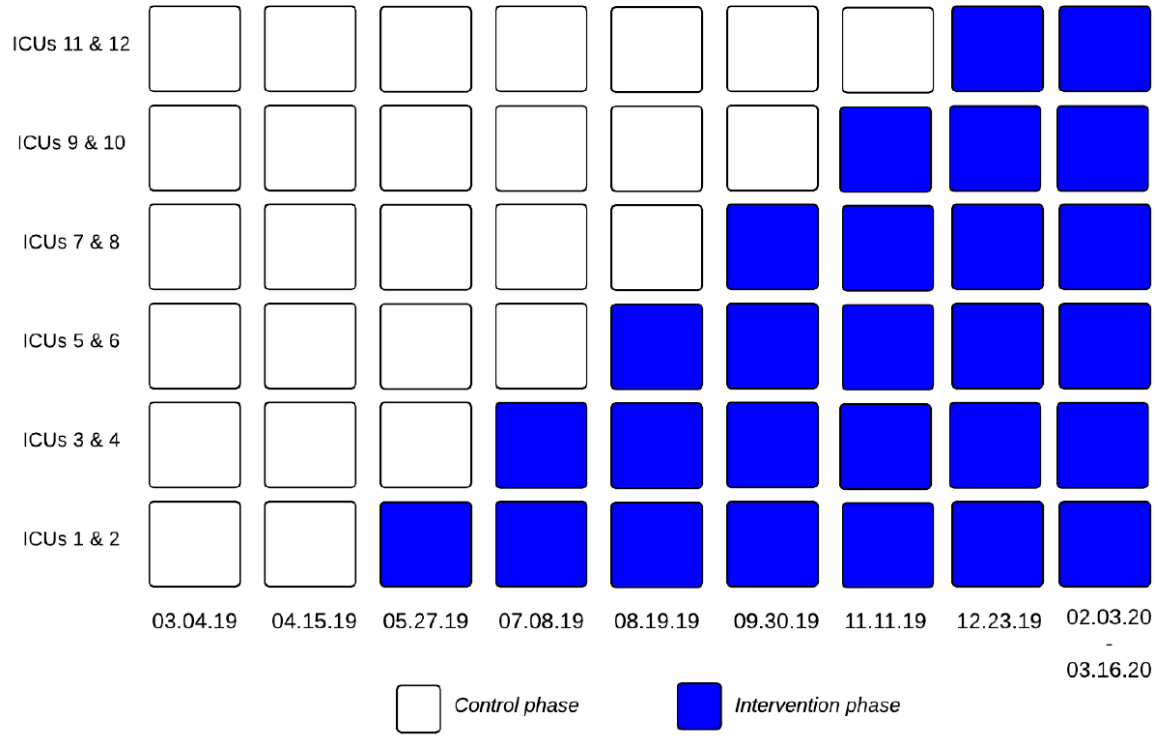
Primary outcome: peak activity (ICU mobility score) within 48 hours of ICU discharge

Key secondary outcomes: ICU & hospital length of stay, mortality, delirium-free days, coma-free days

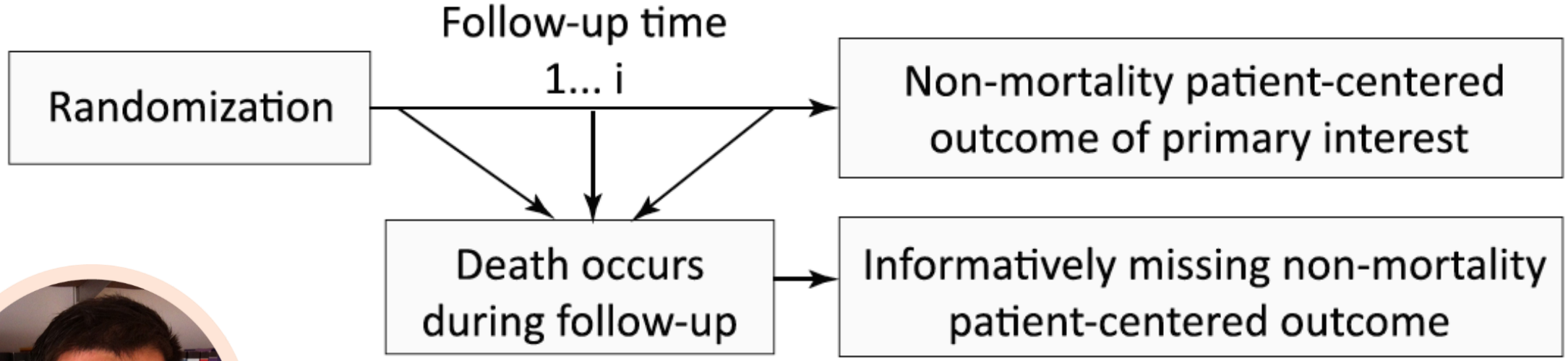
1,917 patients enrolled in %
12 months %

160 patients / month %

$42 / patient %



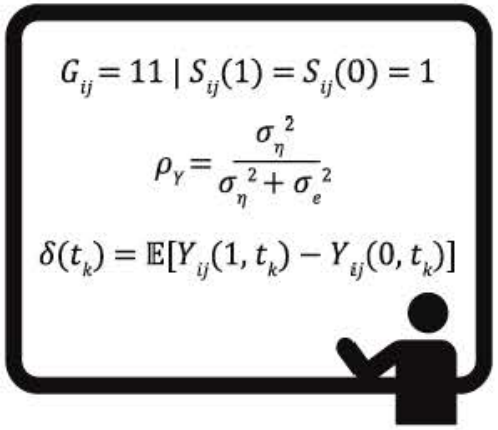
Analyzing outcomes missing due to death in CRTs



Michael Harhay, PhD MS

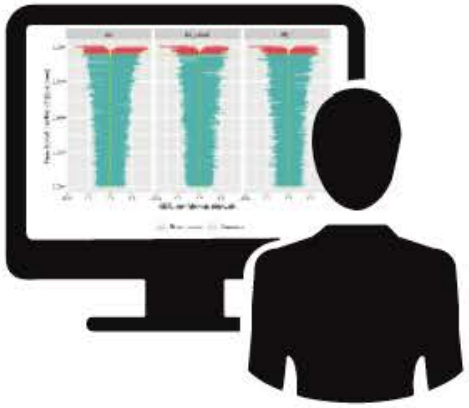
PCORI grant awarded November 2020

Analyzing outcomes missing due to death in CRTs



Aim 1

Develop new approaches to analyze patient-centered data that are missing due to death in cluster-randomized trials.



Aim 2

Compare these new approaches with existing approaches in both statistical simulations and re-analyses of 10 cluster-randomized trials.

Aim 3

Create methodologic guidance that incorporates stakeholder views of desirable qualities of competing approaches alongside technical attributes.

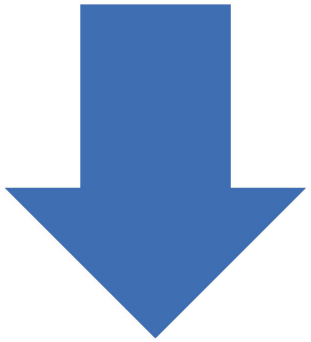
Aim 4

Create and disseminate open-access statistical code and accompanying tutorials to improve patient-centered outcomes research worldwide.

Confessions of an older (but still hopeful) skeptic

Toward Evidence-Based End-of-Life Care

Scott D. Halpern, M.D., Ph.D. N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015



Invited Commentary

Pragmatic Trials and the Evolution of Serious Illness Research

Katherine R. Courtright, MD, MS; Scott D. Halpern, MD, PhD

JAMA Internal Medicine Published online July 6, 2020

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