Design, Conduct and Analysis of Pragmatic Clinical Trials in Palliative Care Research

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Disclosures

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- Ascension Health
- Kaiser Permanente

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ABIM Foundation's
Choosing Wising program

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Learning objectives

- Know how to apply the PRECIS-2 tool

  Loudon K et al, BMJ 2015

- Understand a pragmatic approach in a palliative care trial

  Courtright K et al, AATS 2016

- Pros and cons of an explanatory trial in palliative care

  Carson SS et al, JAMA 2016

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History of Pragmatic Trials

ORIGINAL ARTICLE

J Chronic Dis. 1967.

Explanatory and Pragmatic Attitudes in Therapeutical Trials

Daniel Schwartz, Joseph Lellouch

anté et de la Recherche Medicale, 94 Villejuif, France

JAMA 2003

Practical Clinical Trials

Increasing the Value of Clinical Research for Decision Making in Clinical and

MEDICINE AND PUBLIC ISSUES | 2009 | Annals of Internal Medicine

Clinical Trials for Comparative Effectiveness Transformational Change

, MS; Steven N. Goodman, MD, MHS, PhD; Jason T. Connor, PhD; Sean Tunis, MD, MSc; MD

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

NEJM Aug 2016

Ian Ford, Ph.D., and John Nor

JAMA Guide to Statistics and Methods

JAMA Sept 2016

Pragmatic Trials

Practical Answers to "Real World" Questions

NIH Collaboratory

Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Explanatory vs Pragmatic Trials

ORIGINAL ARTICLE J Chronic Dis. 1967.

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

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What is the trial purpose?

PRAGMATIC STUDY *effectiveness / real world*	EXPLANATORY STUDY *efficacy / ideal conditions*

Doubtless one could solve both problems by running two successive trials when necessary. However, the fact that a trial may easily last for several years emphasises the importance of the initial choice—is one to aim at an immediate increase in knowledge in the hope of eventual practical applications, or at a result which is of immediate applicability but which is less well understood and less fertile for future development?

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Schwartz. J Chronic Dis. 1967.

What is the trial purpose?

PRAGMATIC STUDY *effectiveness / real world*	EXPLANATORY STUDY *efficacy / ideal conditions*

ORIGINAL ARTICLE

A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe[a,*], Merrick Zwarenstein[b], Andrew D. Oxman[c], Shaun Treweek[d], Curt D. Furberg[e], Douglas G. Altman[f], Sean Tunis[g], Eduardo Bergel[h], Ian Harvey[i], David J. Magid[j], Kalipso Chalkidou[k]

J Clin Epi 2009 | doi: 10.1016/j.jclinepi.2008.12.011

The PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon,[1] Shaun Treweek,[1] Frank Sullivan,[2] Peter Donnan,[3] Kevin E Thorpe,[4] Merrick Zwarenstein[5]

BMJ 2015 | doi: 10.1136/bmj.h2147

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PRECIS-2 Domain	PRAGMATIC STUDY *effectiveness / real world*	EXPLANATORY STUDY *efficacy / ideal conditions*
1. Eligibility	All patients	Select patients
2. Recruitment		
3. Setting		
4. Organization		
5. Flexibility (delivery)		
6. Flexibility (adherence)		
7. Follow-up		
8. Primary outcome		
9. Primary analysis		

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PRECIS-2 Domain	PRAGMATIC STUDY *effectiveness / real world*	EXPLANATORY STUDY *efficacy / ideal conditions*
1. Eligibility	All patients	Select patients
2. Recruitment	Occurs within usual care	Intense effort
3. Setting		
4. Organization		
5. Flexibility (delivery)		
6. Flexibility (adherence)		
7. Follow-up		
8. Primary outcome		
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1. Eligibility	All patients	Select patients
2. Recruitment	Occurs within usual care	Intense effort
3. Setting	Random, multiple, diverse	Select, high-performing
4. Organization		
5. Flexibility (delivery)		
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7. Follow-up		
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3. Setting	Random, multiple, diverse	Select, high-performing
4. Organization	Existing resources, processes	Additional resources, training
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6. Flexibility (adherence)		
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5. Flexibility (delivery)	Unscripted, guidelines	Scripted, standardized
6. Flexibility (adherence)	Encouraged	Measured
7. Follow-up		
8. Primary outcome		
9. Primary analysis		

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6. Flexibility (adherence)	Encouraged	Measured
7. Follow-up	Not beyond usual care	Additional, scheduled
8. Primary outcome		
9. Primary analysis		

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6. Flexibility (adherence)	Encouraged	Measured
7. Follow-up	Not beyond usual care	Additional, scheduled
8. Primary outcome	Important to patients	Physiologic, surrogate
9. Primary analysis		

PRECIS-2 Domain	PRAGMATIC STUDY *effectiveness / real world*	EXPLANATORY STUDY *efficacy / ideal conditions*
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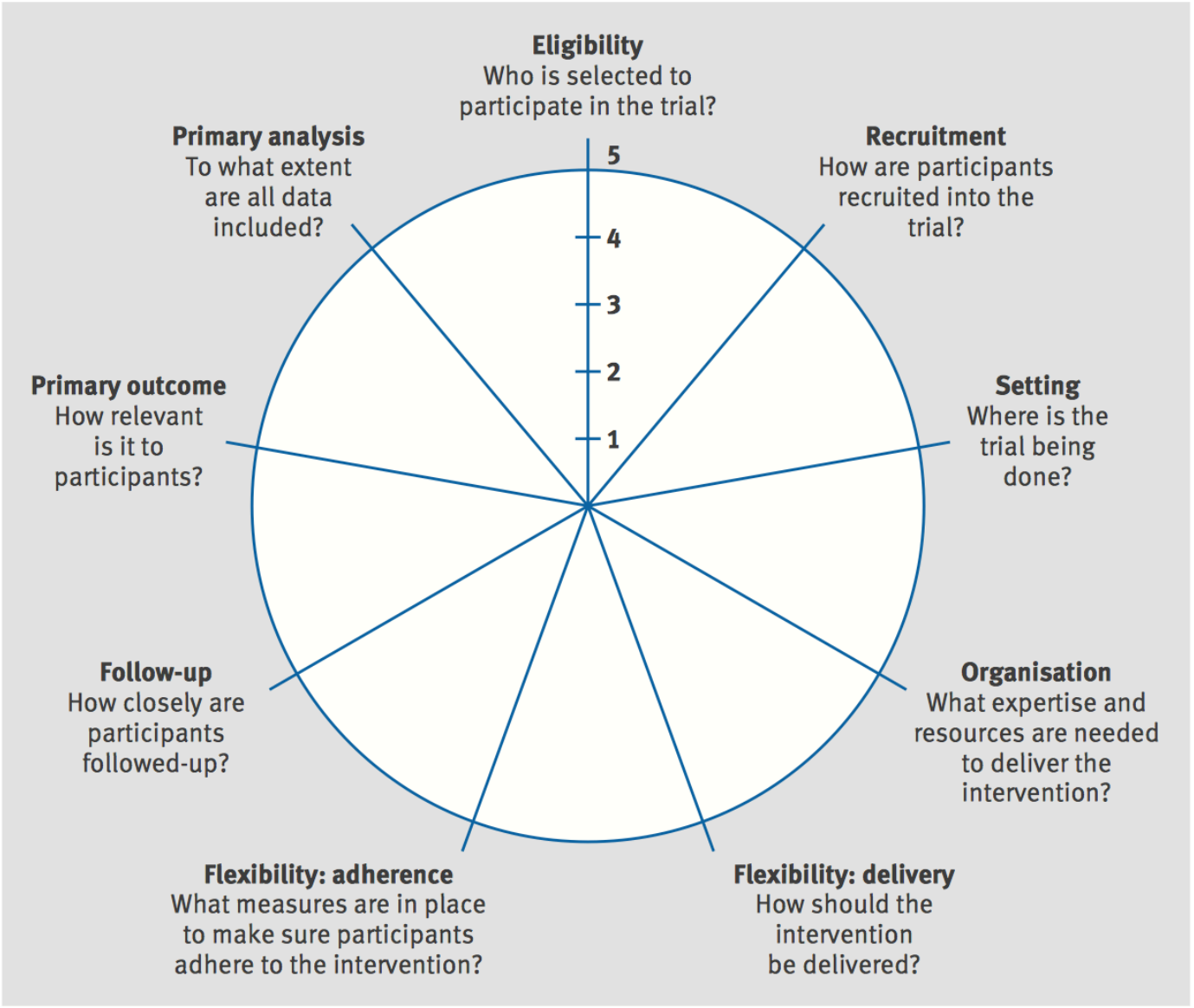
5. Flexibility (delivery)	Unscripted, guidelines	Scripted, standardized
6. Flexibility (adherence)	Encouraged	Measured
7. Follow-up	Not beyond usual care	Additional, scheduled
8. Primary outcome	Important to patients	Physiologic, surrogate
9. Primary analysis	ITT includes all randomized	ITT with exclusions



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

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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]

Ann ATS; Epub 27 Jun 2016 | doi: 10.1513/AnnalsATS.201604-308OT
www.clinicaltrials.gov NCT02505035

Study purpose:

To provide high quality evidence regarding the effectiveness, comparative effectiveness, and costs of inpatient palliative care consult services

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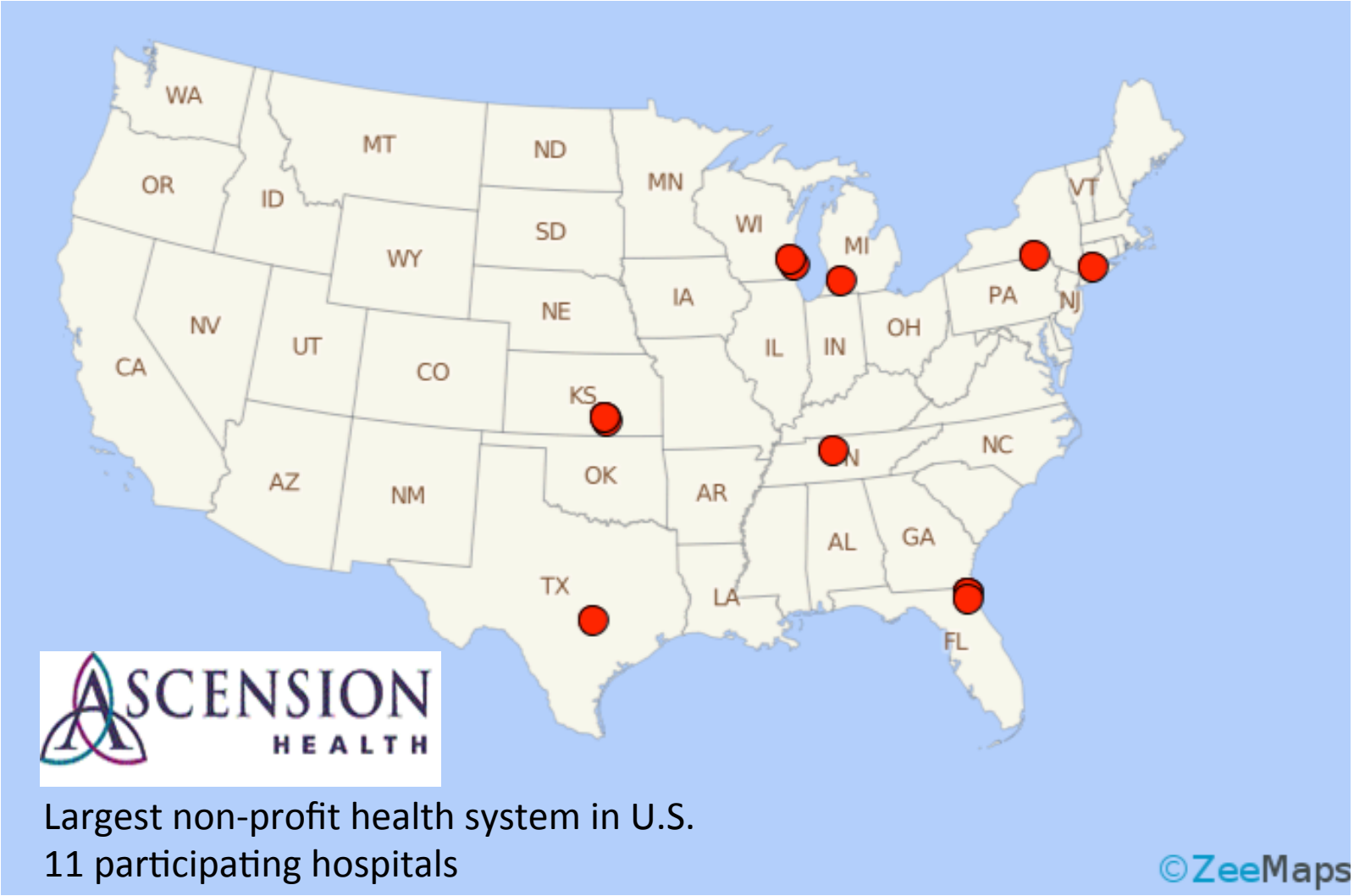
Setting



Largest non-profit health system in U.S.
11 participating hospitals

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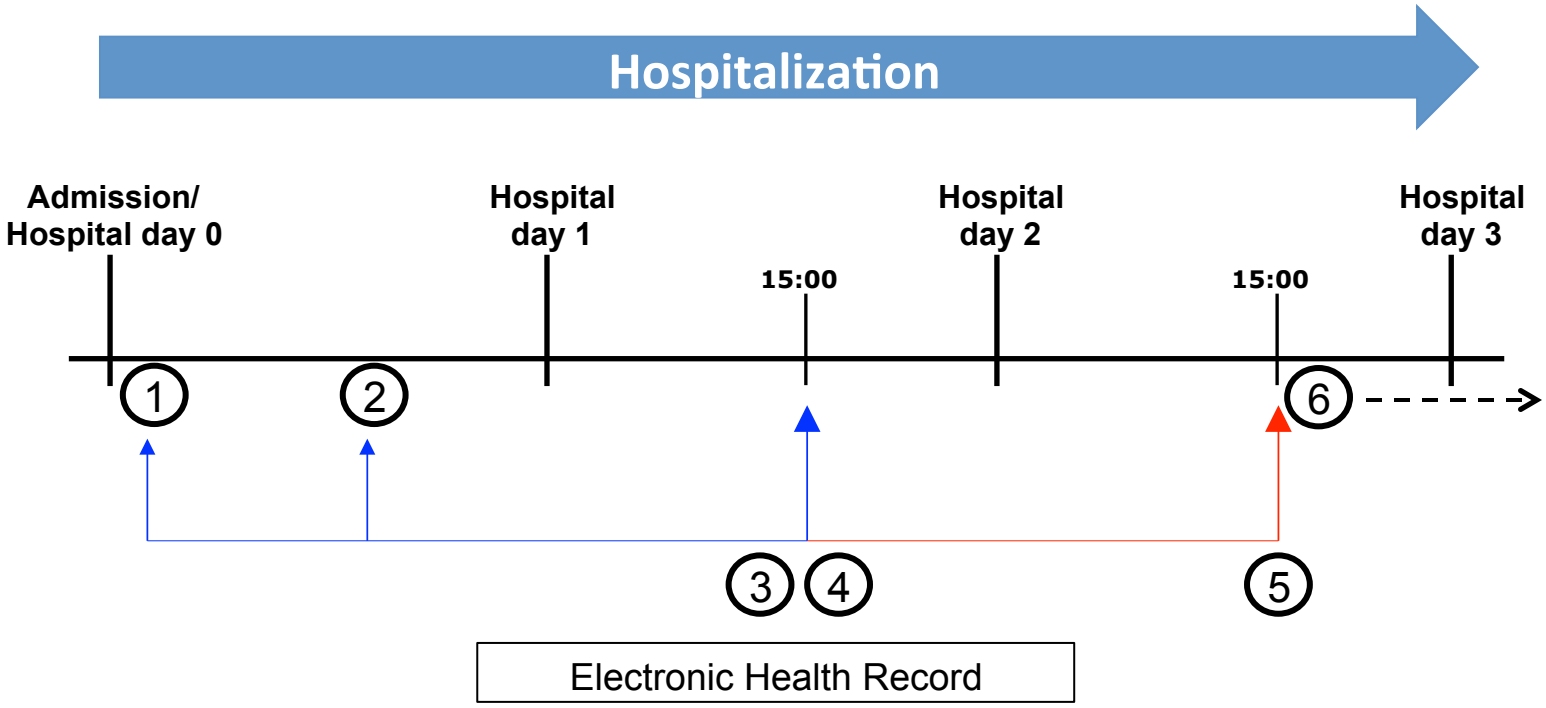
Eligibility

- Age ≥65 years
- Hospital length of stay ≥72 hours
- Consensus criteria: *Weissman and Meier. JPM 2011.*

Life-limiting illness	Secondary criteria
Chronic obstructive pulmonary disease (COPD)	• Oxygen dependence • ≥2 hospitalizations in prior 12 months
End stage renal disease (ESRD)	• Dialysis dependence
Dementia	• Admitted from long-term care facility • ≥2 hospitalizations in prior 12 months • Presence of surgical feeding tube

Recruitment and Organization



1. Admission order is placed
2. Past history form is signed
3. Identification of eligible patients using data mining and/or nursing assessment
4. Eligible patients enrolled in study
5. Default order for consultation (intervention) becomes active if physician doesn't opt-out
6. Palliative care consultation note completed

Flexibility (delivery)

- Actual consultation delivered as per usual care
- Any type of palliative care clinicians
- No additional training required
- Recommended language for palliative care teams to introduce themselves to study patients

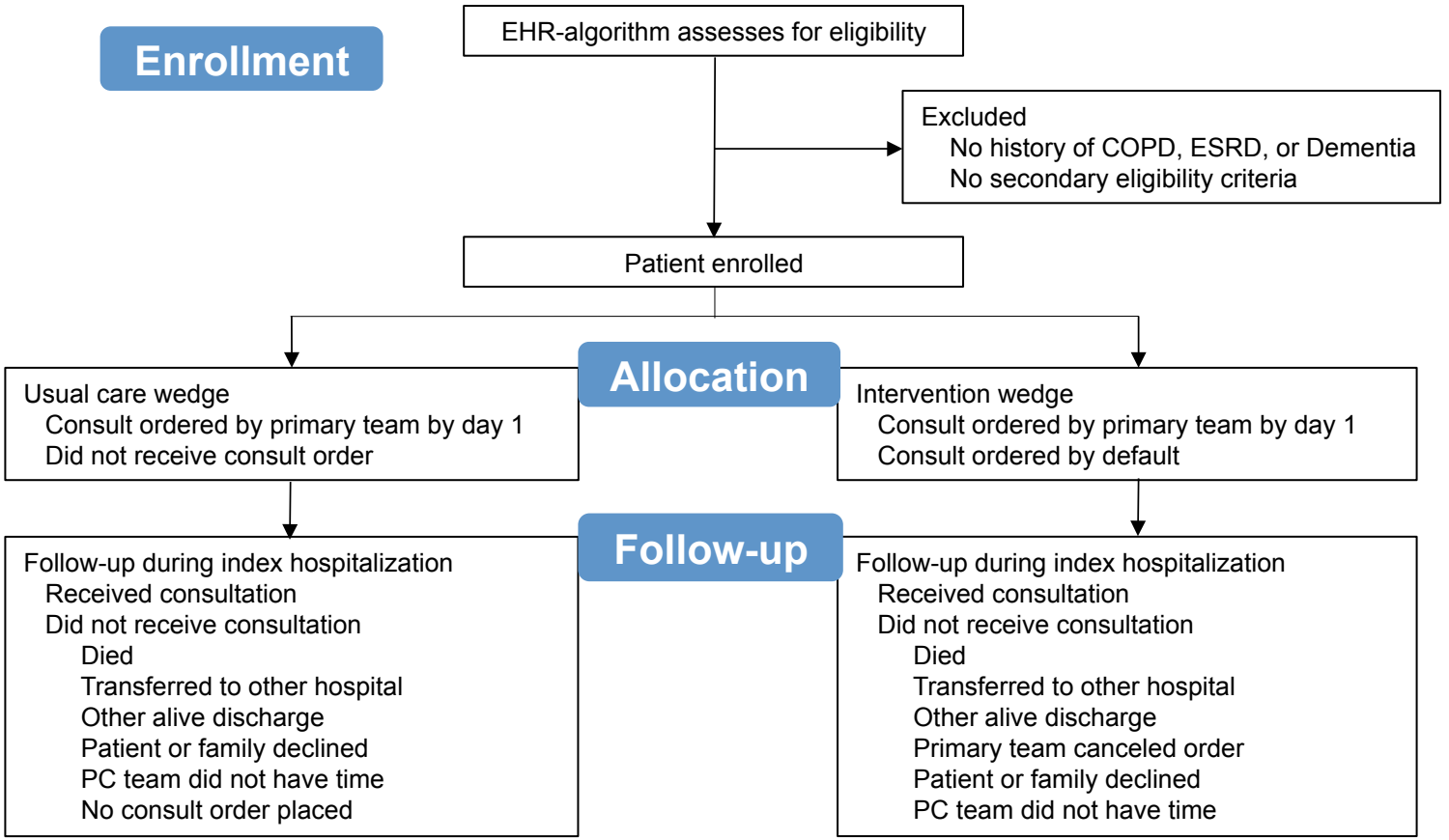
Flexibility (adherence)

1. Leverage mechanisms already in place to encourage nursing completion of electronic eligibility form

2. Track reasons physician cancels default order

3. Do not expect 100% adherence
   - Work with individual palliative care teams to tailor solutions
   - Qualitative survey about consult triage decisions

Follow-up



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Primary outcome and analysis

- Hospital length of stay (with death coded as the longest LOS)
- Intention-to-treat of all randomized patients with LOS ≥72 hours
  - Regardless of adherence to the intervention
- Sensitivity analyses re-coding death at different values along the distribution of LOS

*True pragmatism precludes patient & family-*reported* outcomes in this multicenter, technology-based trial of >18,000 patients*

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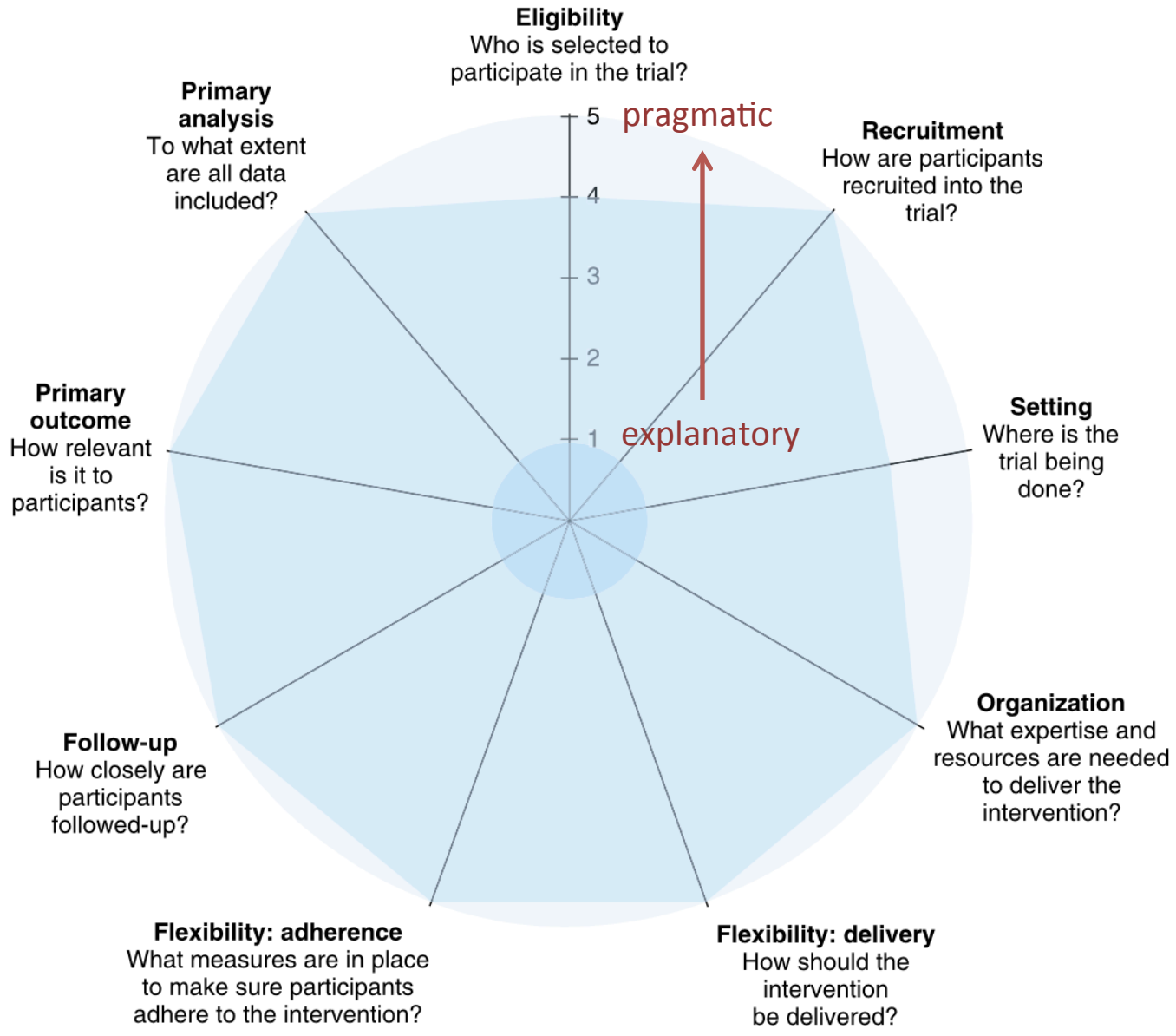
Stat Methods Med Res 2014 | doi: 10.1177/0962280214545121

PRECIS-2 Domain	REDAPS
1. Eligibility	Broad criteria within selected populations
2. Recruitment	Occurs within usual care
3. Setting	Multiple, diverse geography, single health system
4. Organization	Existing resources, processes
5. Flexibility (delivery)	Unscripted, guidelines
6. Flexibility (adherence)	Encouraged
7. Follow-up	Not beyond usual care
8. Primary outcome	Important to patients & other stakeholders
9. Primary analysis	ITT includes all randomized



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Original Investigation

Effect of Palliative Care–Led Meetings for Families of Patients With Chronic Critical Illness

A Randomized Clinical Trial

Shannon S. Carson, MD; Christopher E. Cox, MD, MPH; Sylvan Wallenstein, PhD; Laura C. Hanson, MD, MPH; Marion Danis, MD; James A Tulsky, MD; Emily Chai, MD; Judith E. Nelson, MD, JD

JAMA. 2016;316(1):51-62 | doi:10.1001/jama.2016.8474

Study purpose:

To determine if a palliative care specialist-led communication intervention for families of patients with chronic critical illness can improve both family- and patient-centered outcomes.

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Setting

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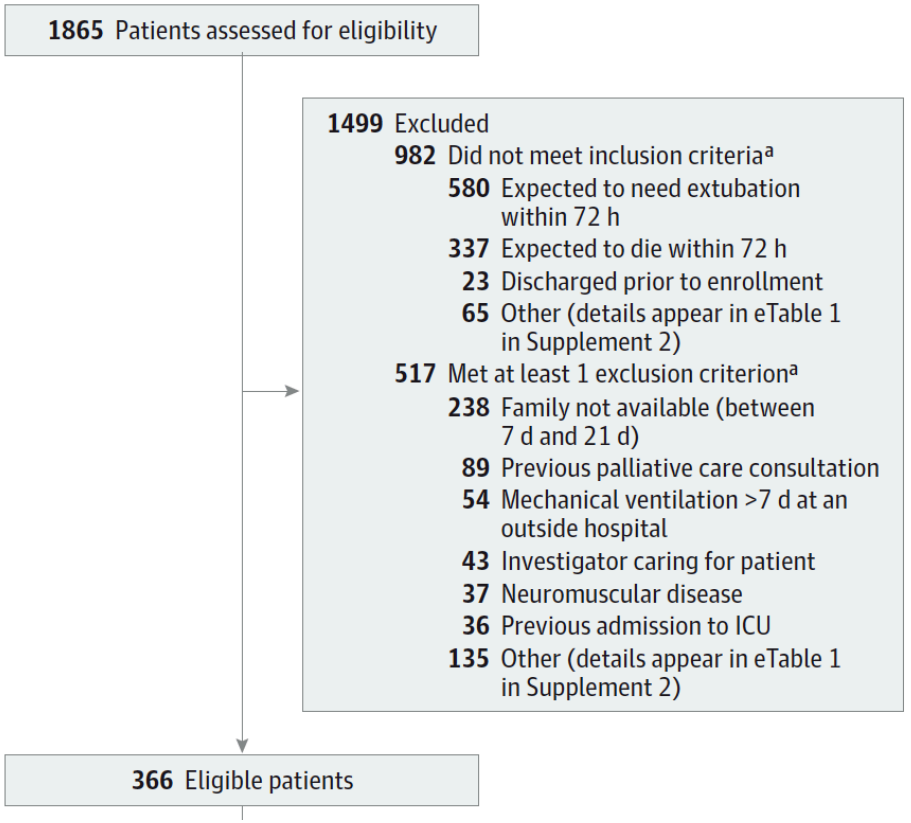
Eligibility

- Medical ICU
- Age ≥21 years old
- Requiring 7 days of mechanical ventilation uninterrupted for ≥96 hours
- Not expected to wean or die within 72 hours

Figure 1. Flow of Patients and Family Surrogate Decision Makers



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Recruitment

a) Recruitment Methods

1. Prelim screen

The source of potential subject Intensive Care Unit. The research coordinator will conduct a focused screening. Each weekday, one Research Assistant (RA-1) at each site will screen for potential subjects by asking the ICU clinical team to identify patients meeting eligibility criteria. The ICU clinicians (the primary doctor for this patient) will identify patients that are likely to be eligible for

2. Final screen

Verification of eligibility through the medical record will be limited to the length of mechanical ventilation and absence of trauma, burn, and neuromuscular diseas

3. Approach participants

describe the study to surrogates of patients who are eligible, as well as patients informed consent (we do not expect that patients will have such capacity because they will be critically ill and mechanically ventilated) a

4. Assess capacity

search coordinator to the patient and family. No identifiable information will be retained. Patient capacity for consent will be evaluated by the ICU attending physician, who will consult about the patient's capacity with the research assistant and the patient's bedside nurse. Capacity of surrogates to provide consent will be evaluated by the ICU attending physician. We will be offering study participation to two categories of surrogates: 1) Primary Surrogate and 2) Additional I

5. Approach participants

The ICU attending physician will introduce the Research Assistant to potential participants, from whom the Research Assistant will seek informed research consent after a full explanation of the study.

6. Informed consent

Research assistant task

ICU clinician task

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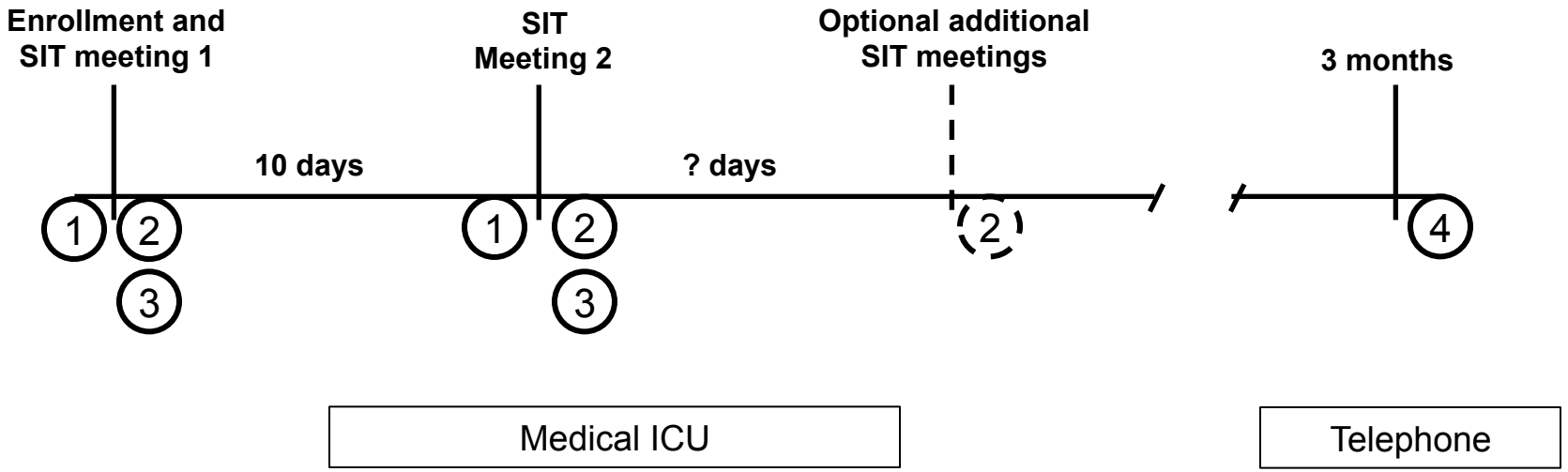
Organization



1. Pre-Supportive Information Team (SIT) meeting between SIT team and ICU team
2. SIT team coordinated and conducted family meeting
3. Survey administration*: Hospital Anxiety and Depression Scale, ACP domain of After-Death Bereavement Family Interview, Quality of Communication Scale
4. Outcomes collection*: Hospital Anxiety and Depression Scale, Impact of Events Scale-Revised, Family Satisfaction in the ICU Survey

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*Surveys administered by different research assistants as each time point blinded to randomization arm

Flexibility (delivery)

- Interdisciplinary palliative care team with additional certifications in EOL and family communication skills
- Palliative care physician and advanced practice nurse required at each SIT meeting, led by physician
- All participants received “intensive and specific training on the meeting protocol from expert faculty”
- “Protocolized approach” to family meetings

Flexibility (adherence)

1. Corrective re-training of SIT team members as needed

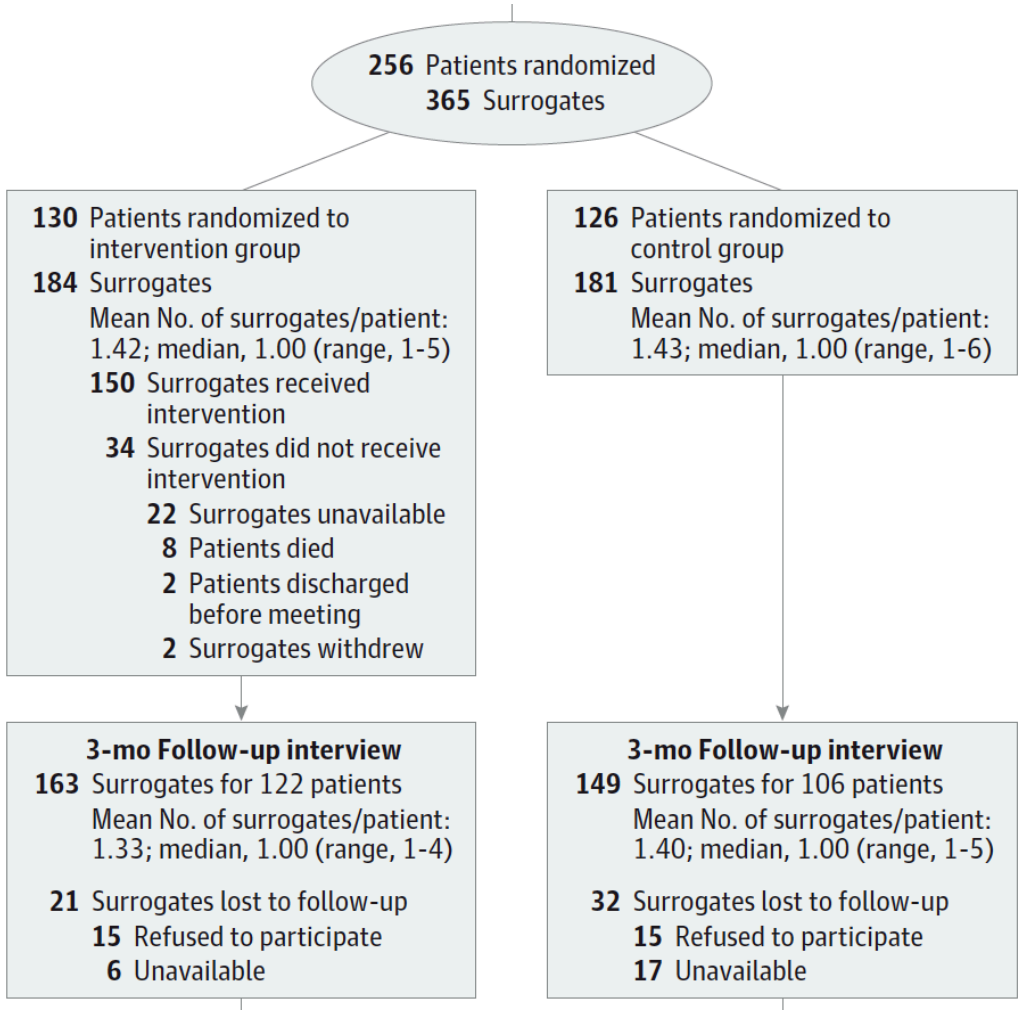
2. Regular audits at each site of family meeting audio and completed meeting template forms

eTable 2: Fidelity to items in structured Support and Information Team (SIT) meetings (n=176)

SIT Meeting Topics Covered, No. (%)	**SIT-1** (n = 112)	**SIT-2** (n = 64)
Introduction of Participants	112 (100)	64 (100)
Patient's Condition	112 (100)	64 (100)
Patient's Prognosis	112 (100)	58 (91)
→ Alternatives to Continued Intensive Care Therapy	52 (46)	22 (34)
→ Care Settings for Chronically Critically Ill Patients (SIT-1 only)	64 (57)	----
→ Patient Advance Directive	72 (64)	26 (41)
Likely Discharge Options (SIT-2 only)	----	47 (75)
Patient's Likely Care Needs (SIT-2 only)	----	47 (75)
Family Summarized Discussion	72 (64)	45 (70)
Family's Understanding of Patient's Values/Goals/Preferences	100 (89)	52 (81)
→ Plan for Follow Up with the Responsible MD	72 (64)	38 (60)
Plan for Follow Up with SIT Clinicians	88 (79)	24 (38)

Follow-up

- 1 time point
- Via telephone
- ≤30 min surveys
- 2 reminder letters



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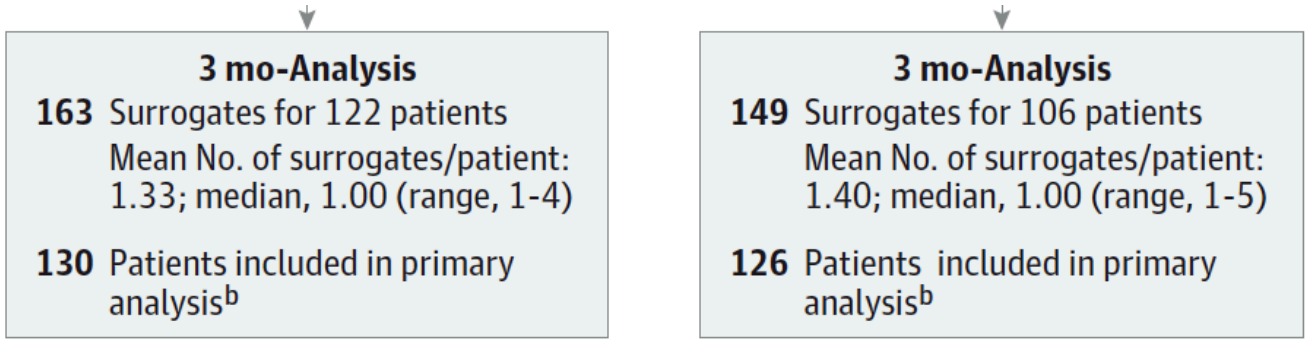
Primary outcome and analysis

- 90-d surrogate-reported hospital anxiety and depression scale
- (modified?) intention-to-treat of all randomized patients



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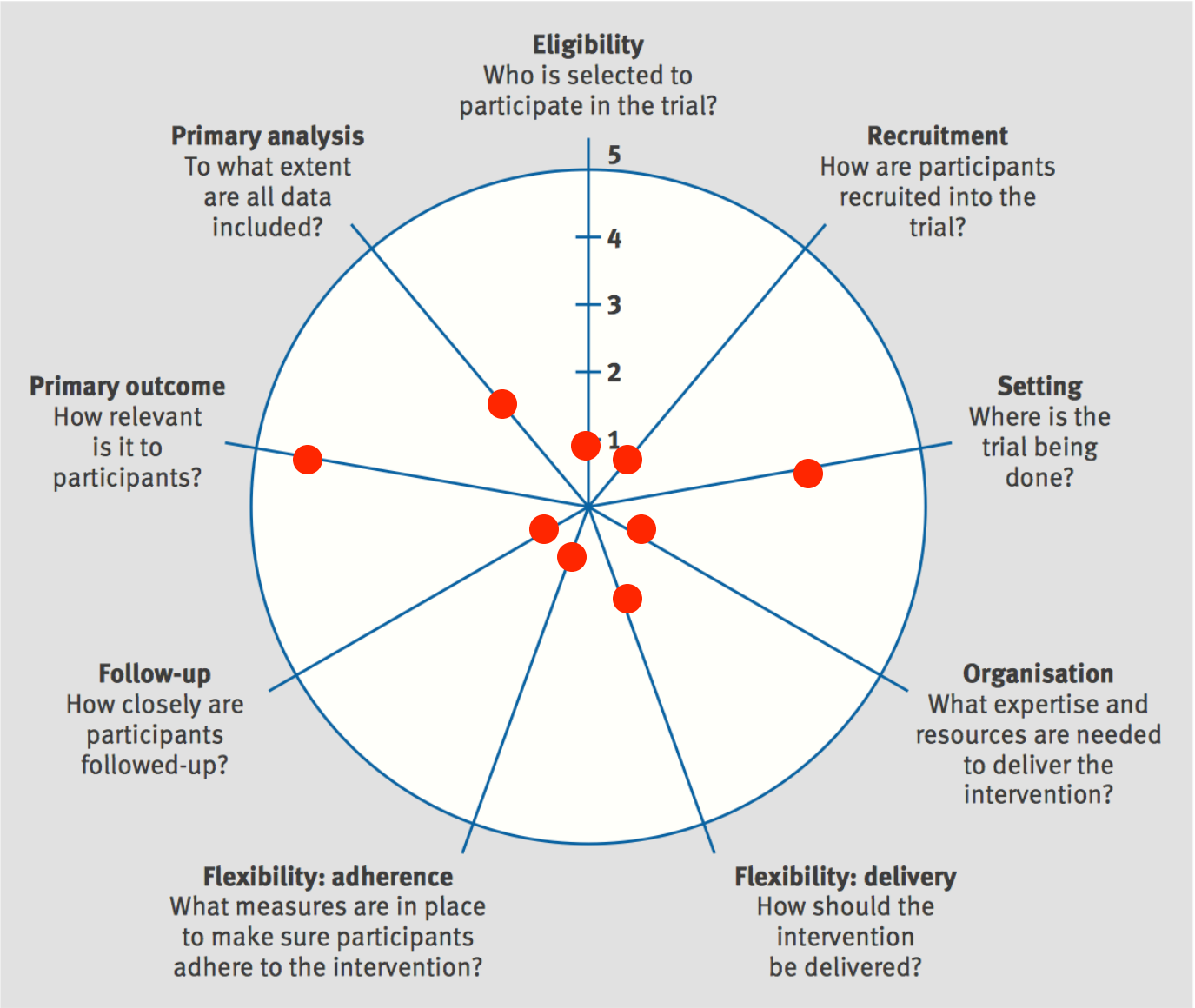
PRECIS-2 Domain	REDAPS	Carson et al. JAMA. 2016
1. Eligibility	Broad criteria within selected populations	Narrowly selected population, many exclusion criteria
2. Recruitment	Occurs within usual care	Outside of usual care
3. Setting	Multiple, diverse geography, single health system	Multiple, diverse geography, not randomly selected
4. Organization	Existing resources & processes	Additional personnel, new process
5. Flexibility (delivery)	Unscripted, guidelines	Scheduled, scripted guidelines
6. Flexibility (adherence)	Encouraged, tracked	Audits, re-training
7. Follow-up	Not beyond usual care	3-mo follow-up surveys
8. Primary outcome	Important to patients & other stakeholders	Important to patients & families
9. Primary analysis	ITT includes all randomized	ITT excludes lost to follow-up



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

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Conclusions

- Pragmatic vs Explanatory: what is the trial purpose?
- Use PRECIS-2 criteria as a guide during study design
- Potential limitations relevant to palliative care:
  - Pragmatic – heterogeneous intervention, data collection
  - Explanatory – simple inflexible intervention, homogenous population