Pragmatic Trials

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NIH National Institute on Aging

Outline of talk

- Definitions
- Rationale for pragmatic trials
- How to assess “pragmatic-ness”
- Examples: MIFREE, PROVEN
- Nuts & Bolts of design

NIH spends $3 Billion/yr on clinical trials

- “NIH must ensure that supported trials investigate a mission-relevant question that is of high priority, do not needlessly duplicate previously conducted trials (in contrast to providing needed replication), and have the highest likelihood to advance knowledge and improve health.”

Opinion

VIEWPOINT

Toward a New Era of Trust and Transparency in Clinical Trials

Kathy L. Hudson, PhD
National Institutes of Health, Bethesda, Maryland.

Michael S. Lauer, MD
National Institutes of Health, Bethesda, Maryland.

Francis S. Collins, MD, PhD
National Institutes of Health, Bethesda, Maryland.

Clinical trials are the most publicly visible component of the biomedical research enterprise, from the potential human application of novel laboratory findings to the generation of robust evidence about treatments or preventive interventions in routine clinical care. These trials are also the point at which biomedical research most directly engages human participants—dedicated volunteers who trust investigators to uphold the highest standards of scientific rigor and ethical oversight. While clinical trials have evolved and improved over time—producing impressive advances in diagnosis, treatment, and prevention—there are still major challenges. Therefore, fundamental changes are needed to reflect science and society's movement to increase efficiency, accountability, and transparency in clinical research.

The aim is to help ensure that all involved in the clinical trial enterprise have the appropriate knowledge about the design, conduct, monitoring, recording, analysis, and reporting of clinical trials. While GCP training on its own may not be sufficient, it provides a consistent and high-quality standard.

Another important change at the beginning of the clinical trial lifecycle is a new NIH policy that will require all applications for clinical trials to be submitted in response to clinical trial–specific Funding Opportunity Announcements (FOAs). This will mean that applications including one or more clinical trials will no longer be accepted in response to parent funding announcements, which are broad FOAs that allow researchers to submit investigator-initiated applications without specific ele-

Hudson, Lauer, Collins. *JAMA*. Published online September 16, 2016. doi:10.1001/jama.2016.14668

NIH Definitions

- *Clinical Trial:* research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
- *Intervention:* manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
  - Examples include: drugs/small molecules/compounds; biologics; devices; procedures; delivery systems; strategies to change health-related behavior; treatment strategies; prevention strategies; and, diagnostic strategies.

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

ORIGINAL CONTRIBUTION

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD
Deborah A. Zarin, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was

Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and [Data Monitoring Committees].

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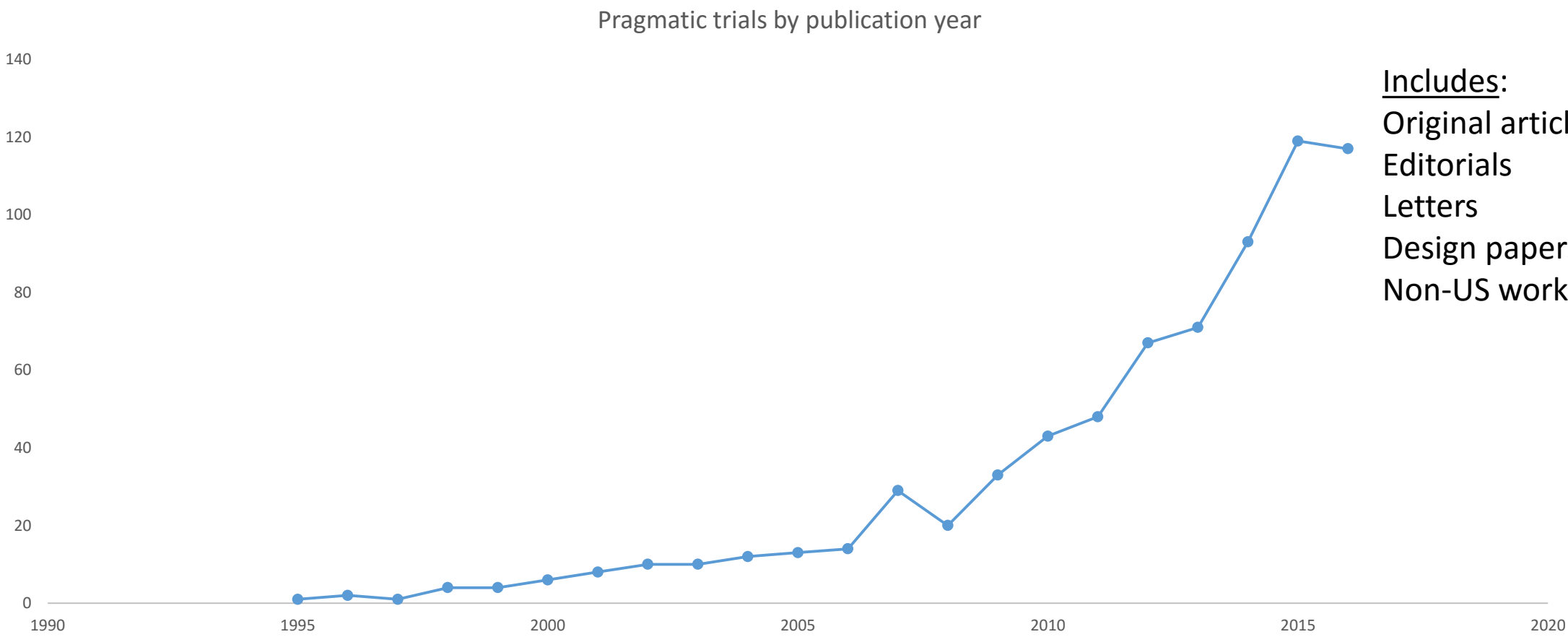
JAMA. 2012;307(17):1838-1847 www.jama.com

policy, which took effect in 2005, of requiring registration of clinical trials as a prerequisite for publication.[6,7] The Food and Drug Administration Amendment Act (FDAAA)[8] expanded the mandate of

Rise of Pragmatic Trials



Includes:
Original articles
Editorials
Letters
Design papers
Non-US work

Articles per year catalogued in MEDLINE that have in the title or abstract the words pragmatic or naturalistic and the word trial.

Which Treatment is Best for Whom?

High-Quality Evidence is Scarce

< 15% of guideline recommendations supported by high quality evidence

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

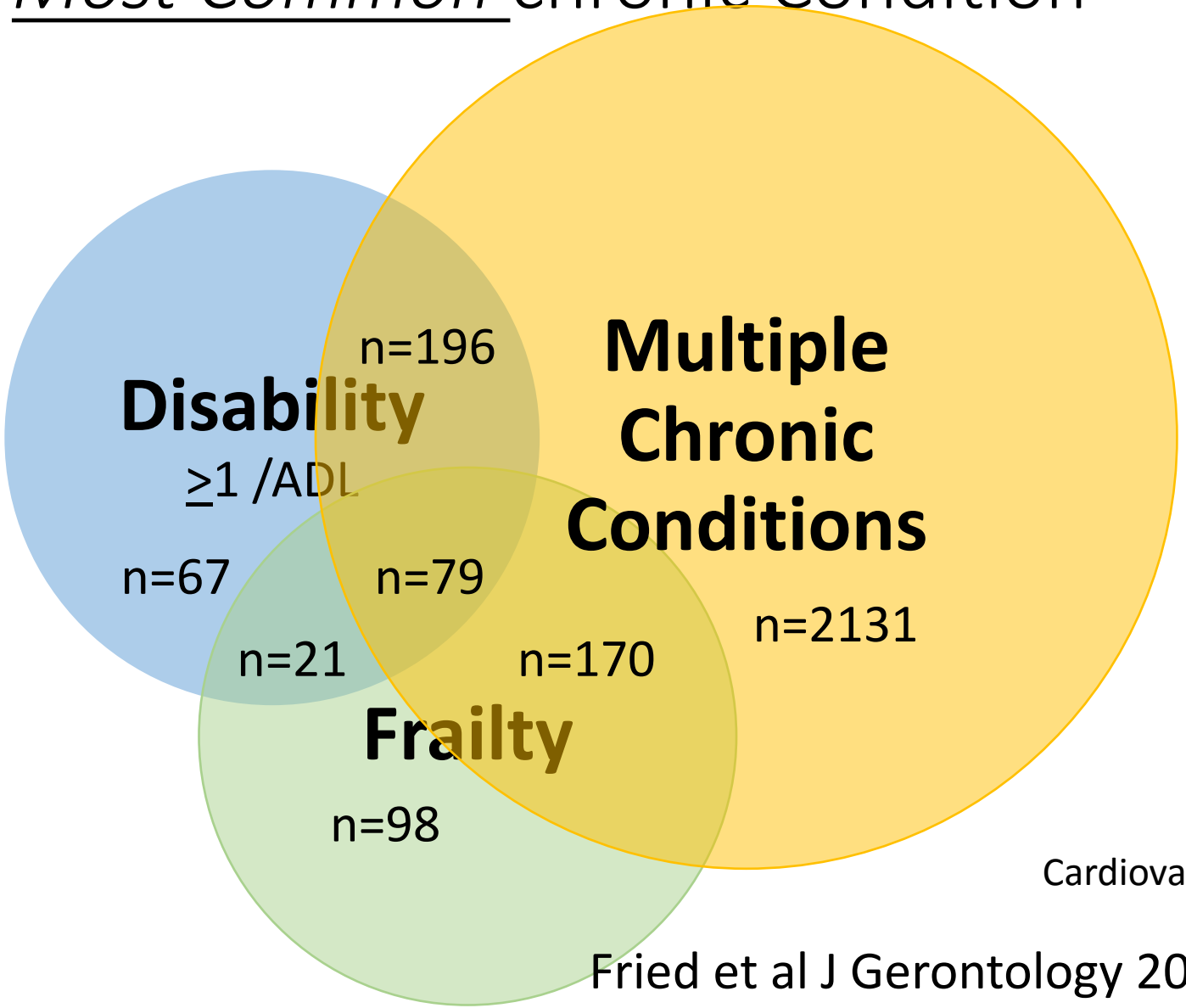
Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Tricoci P et al. JAMA 2009;301:831-41

MCC: *Most Common* chronic Condition



N=2762 overall
Age 65+ M/F
Cardiovascular Health Study

Fried et al J Gerontology 2001;56A:M146.

General Classification

- Explanatory trials
  - Intent to evaluate a biological or mechanistic hypothesis
- Pragmatic trials
  - Intent to inform decision makers about health and healthcare

Elements of PCTs

- Compare clinically relevant alternatives
- Enroll diverse study population
- Recruit from a variety of practice settings
- Measure a broad range of relevant health outcomes
    - Tunis, Stryer and Clancy JAMA

Practical Adaptation of PCT Definition

(1) an intent to inform decision-makers (patients, clinicians, administrators, and policymakers), as opposed to elucidating a biological or social mechanism;

(2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant; and

(3) either an intent to

- *(a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial*
- *(b) measure a broad range of outcomes*

Pragmatic Clinical Trial

Fit for the purpose of informing decision-makers regarding the comparative balance of benefit and risk of a biomedical or behavioral health intervention at the individual or population level

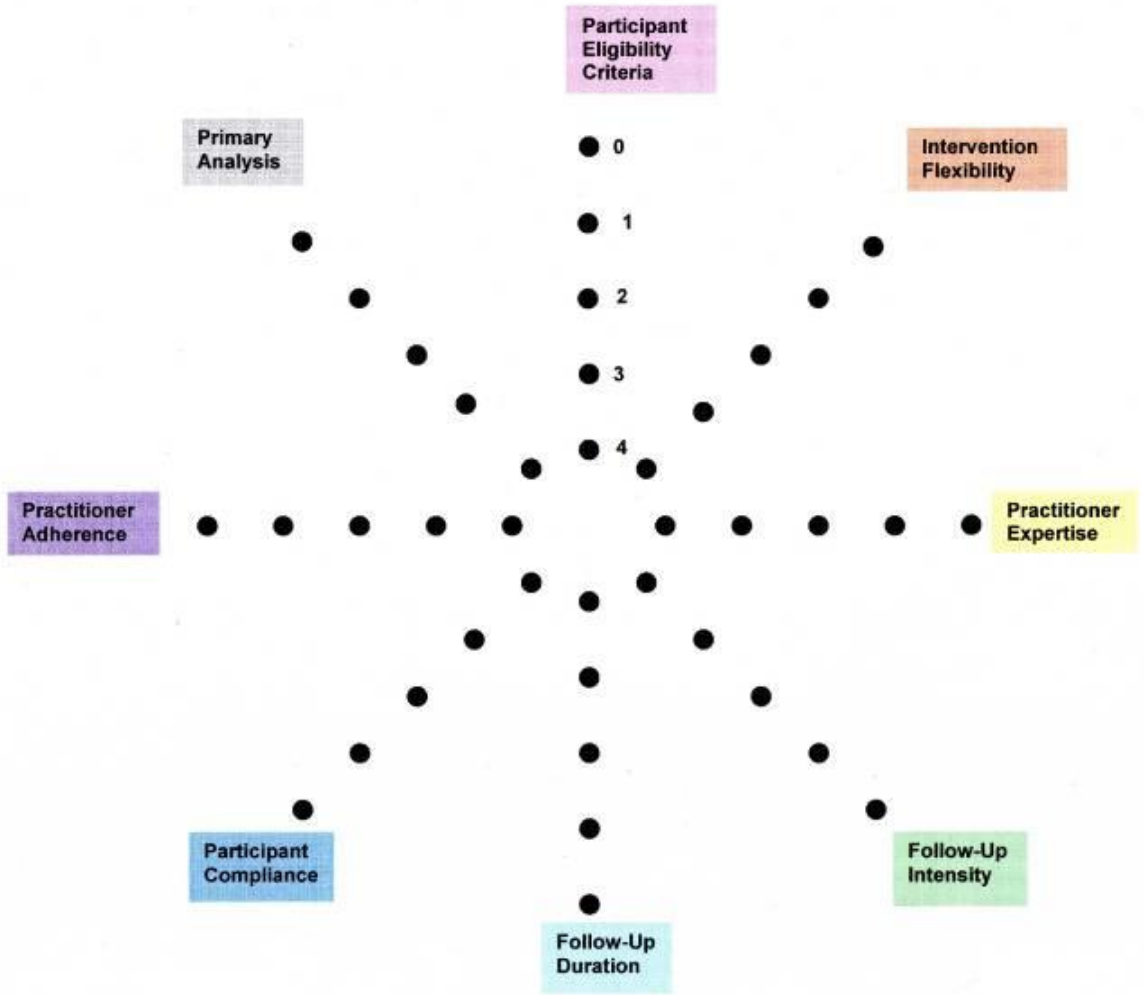
“We should be striving for pragmatism in every clinical trial.”

Robert M Califf MD, FDA Commissioner

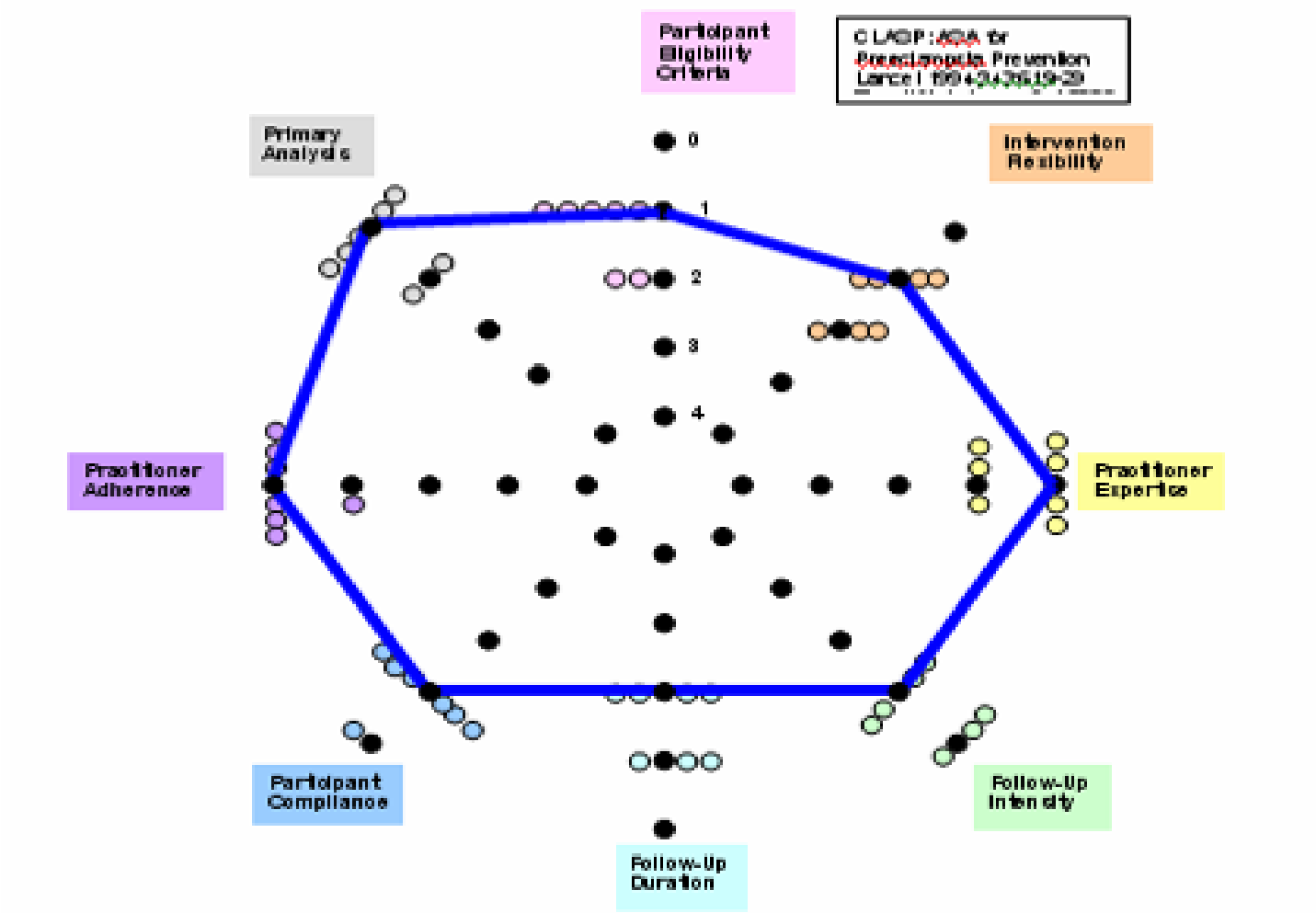
Pragmatic	vs	Explanatory
Broad eligibility		Narrow eligibility
Flexible interventions		Strict instructions
Typical practitioners		Expert practitioners
No follow-up visits		Frequent follow-up visits
Objective clinical outcome		Surrogate outcomes
Usual compliance		Close monitoring
Intent-to-treat		ITT plus per protocol

Thorpe KE et al. CMAJ 2009;180:E47

The PrECIs Spokes
Pragmatic-Explanatory Continuum Indicators

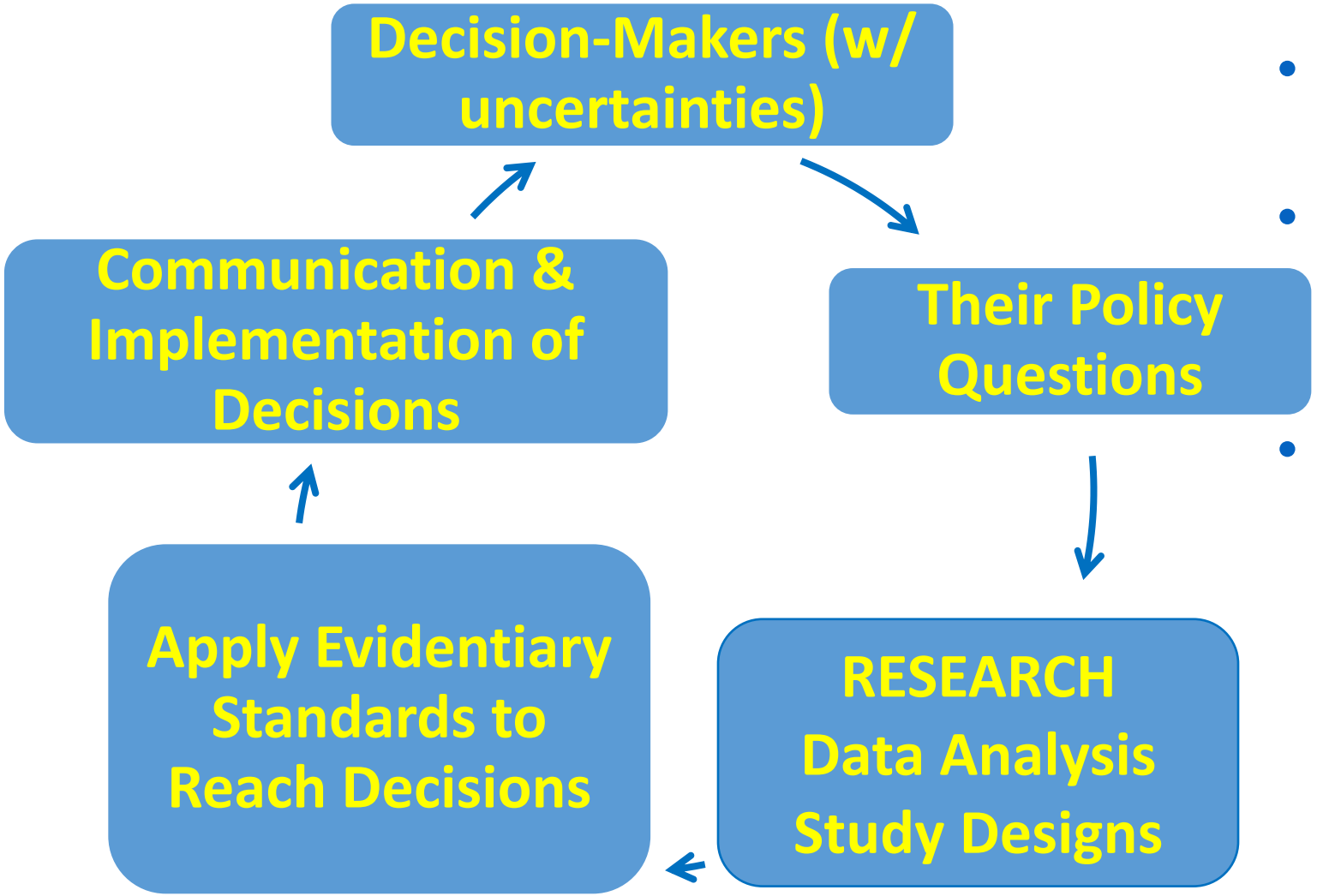


Example: The CLASP Trial



www.unicem-web.org/support/precis.ppt

Evidence-based Decision-Making in Medicare



- Should we pay for this service? = Coverage
- Did we pay the right amount for service? = Payment
- Was the service performed optimally? = Quality

Garrison LP et al. *Health Affairs* 2010;30:1812-1817.

Evidence-based Decision-Making in Medicare (2)

- Coverage based on “reasonable & necessary”
- Sufficient level of confidence that evidence is adequate to conclude that the item or service:
  - improves health outcomes
  - generalizable to the Medicare population.

Recent Medicare Coverage Decisions

Recognize low quality existing evidence

Desire additional real-world evidence

- “Coverage with Evidence Development” paradigm for coverage of an item or service only in the context of a clinical study, e.g.:
  - Percutaneous Left Atrial Appendage (LAA) Closure Therapy
  - Transcatheter aortic valve replacement
  - Amyloid Positron Emission Tomography
  - Allogeneic hematopoietic stem cell transplantation (HSCT) for
    - Multiple Myeloma,
    - Myelofibrosis, and
    - Sickle Cell Disease

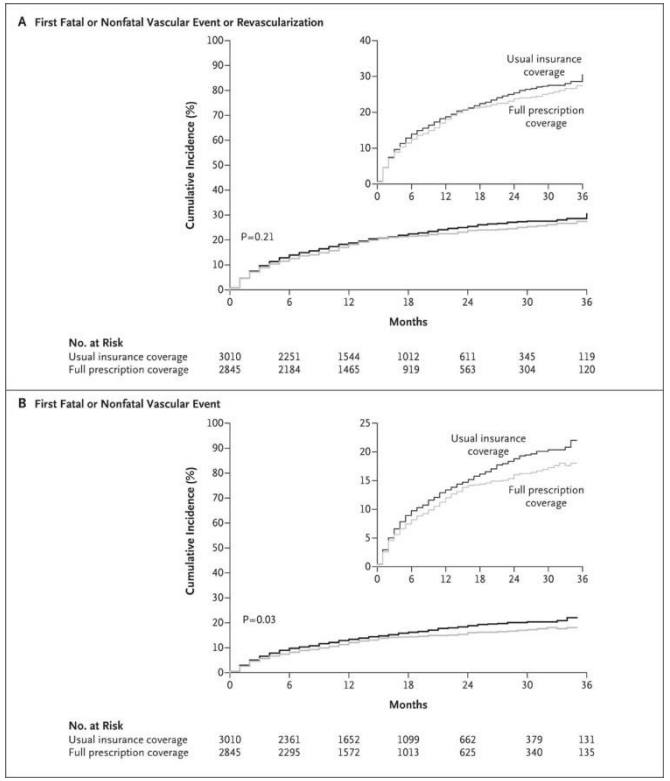
https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html

MIFREE: Full Coverage for Preventive Medications after Myocardial Infarction (MI)

- Enrolled 5,855 patients to test whether eliminating copayments for medications after hospitalization for MI would affect health outcomes or adherence.
- Enhanced prescription coverage improved medication adherence and rates of first major vascular events and decreased patient spending without increasing overall health costs.
- Aetna, the trial sponsor, implemented the findings at the time of trial publication, for all beneficiaries.

Choudry NK et al. N Engl J Med 2011; 365:2088-2097

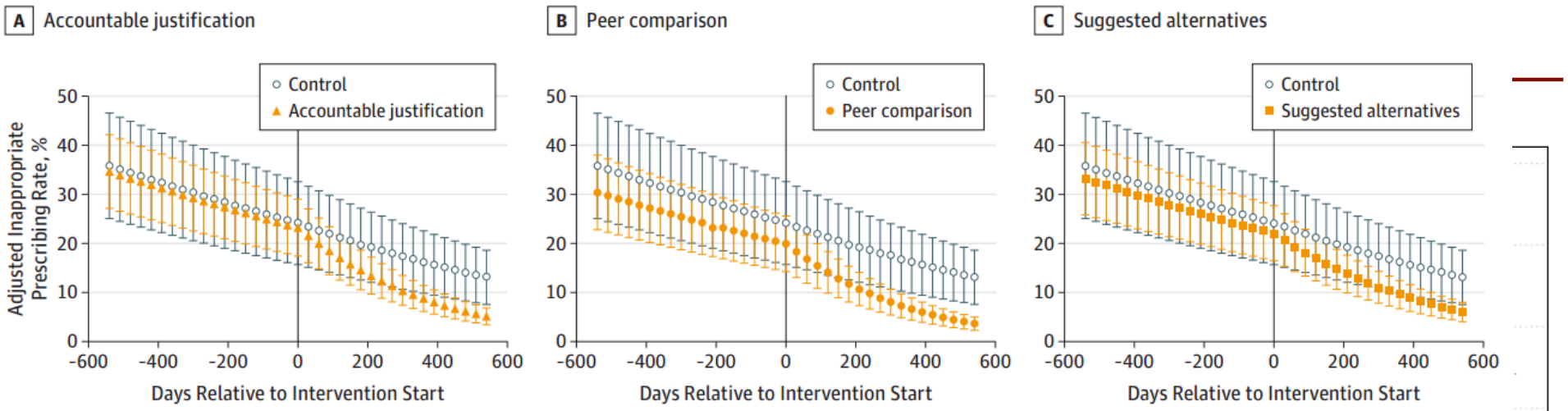
Main Results



The NEW ENGLAND JOURNAL of MEDICINE

Antibiotics Trial: Nudges Lead to Reduction in Inappropriate Antibiotics Rx

Figure 2. Adjusted Rates of Antibiotic Prescribing at Primary Care Office Visits for Antibiotic-Inappropriate Acute Respiratory Tract Infections Over Time



Original Investigation

Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices

A Randomized Clinical Trial

JAMA The Journal of the American Medical Association

Daniella Meeker, PhD; Jeffrey A. Linder, MD, MPH; Craig R. Fox, PhD; Mark W. Friedberg, MD, MPP; Stephen D. Persell, MD, MPH; Noah J. Goldstein, PhD; Tara K. Knight, PhD; Joel W. Hay, PhD; Jason N. Doctor, PhD

JAMA. 2016 Feb 9;315(6):562-70. doi: 10.1001/jama.2016.0275. Grant RC4 AG039115

PROVEN

PRagmatic Trial of Video Education in Nursing Homes

- **OBJECTIVE: To conduct a pragmatic cluster RCT of Advance Care Planning video intervention in NH patients with advanced comorbid conditions in 2 NH health systems (Genesis, PruittHealth) (230 NHs)**

BROWN
School of Public Health

Institute for Aging Research
Hebrew SeniorLife

HARVARD MEDICAL SCHOOL

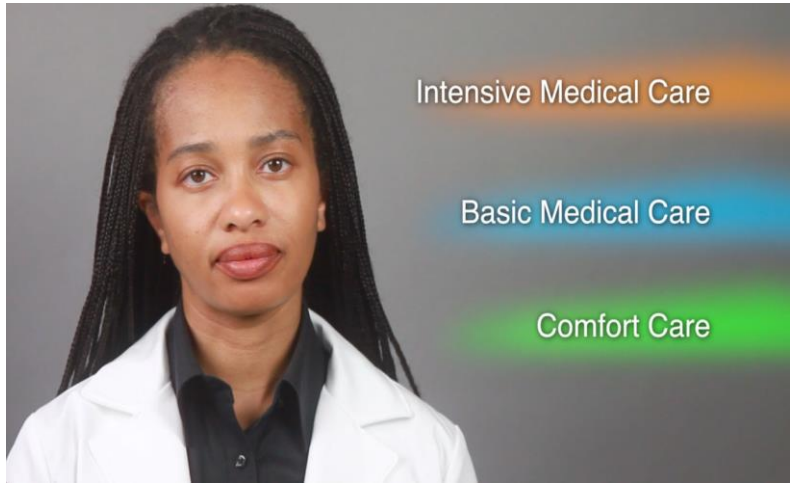
MGH 1811

Background: PROVEN trial

- NHs are complex health care systems
  - 3 million patients admitted annually
  - Rapidly growing % post-acute care
- Patients medically complex with advanced comorbid illness
- Advance care planning (ACP)
  - *Process* of communication
  - Align care with preferences
  - Leads to advance directives (e.g., DNR, DNH)
- Better ACP associated with improved outcomes
- Reality is that ACP is under-utilized

Background: ACP videos

- Options for care with visual images
- Broad goals of care
  - Life prolongation, limited, comfort
- Specific conditions/treatments
- Adjunct to counseling
- 6-8 minutes
- Multiple languages



Background: ACP videos

- Tested in many 'explanatory' RCTs
  - Advanced dementia, Advanced cancer, hospitalized general medicine patients
    - *BMJ 2009; J Clin Onc 2010; J Clin Onc 2013; JGIM 2015*
  - Outcomes mostly limited to immediate preferences, not care
- State-wide Hawaii implementation
  - 11hospitals, 50 NHs, 9 hospices, 14 out-patient
  - "Real-world" experience
  - No consistent infrastructure or formal evaluation

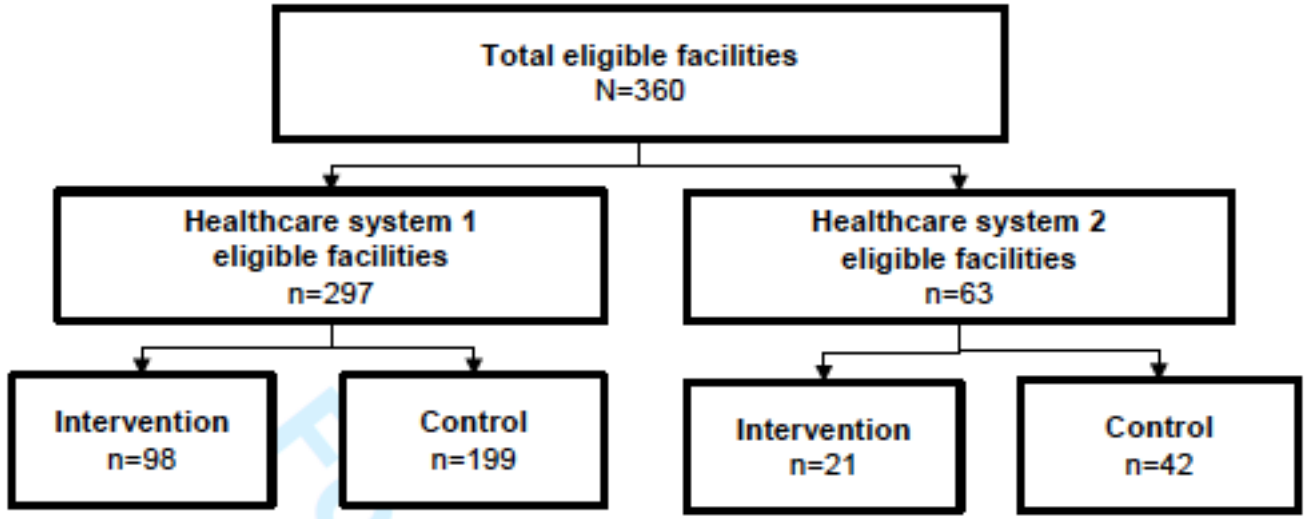
PROVEN: Setting

Characteristics of partner NH Health Systems		
Characteristic	Genesis	PruittHealth
Facilities, No.	406	92
States, No.	28	4
EMR system	PointClickCare™	American Health Tech

- **Based on Power Calculations**
  - **230 Facilities Total (115/arm)**

Final Sample Size of PROVEN Facilities by Health System

Figure 1. Stratification and randomization of nursing home facilities



PROVEN: Intervention

- 18 month intervention period
- Suite of 5 ACP videos
  - Goals of Care, Advanced Dementia, Hospitalization, Hospice, ACP for Healthy Patients
- Offered facility-wide
  - All new admits, care-planning meetings for long-stay, readmission
- Flexible (who, how, which video)
- Tablet devices, internet
- Training: corporate level, webinars, toolkit

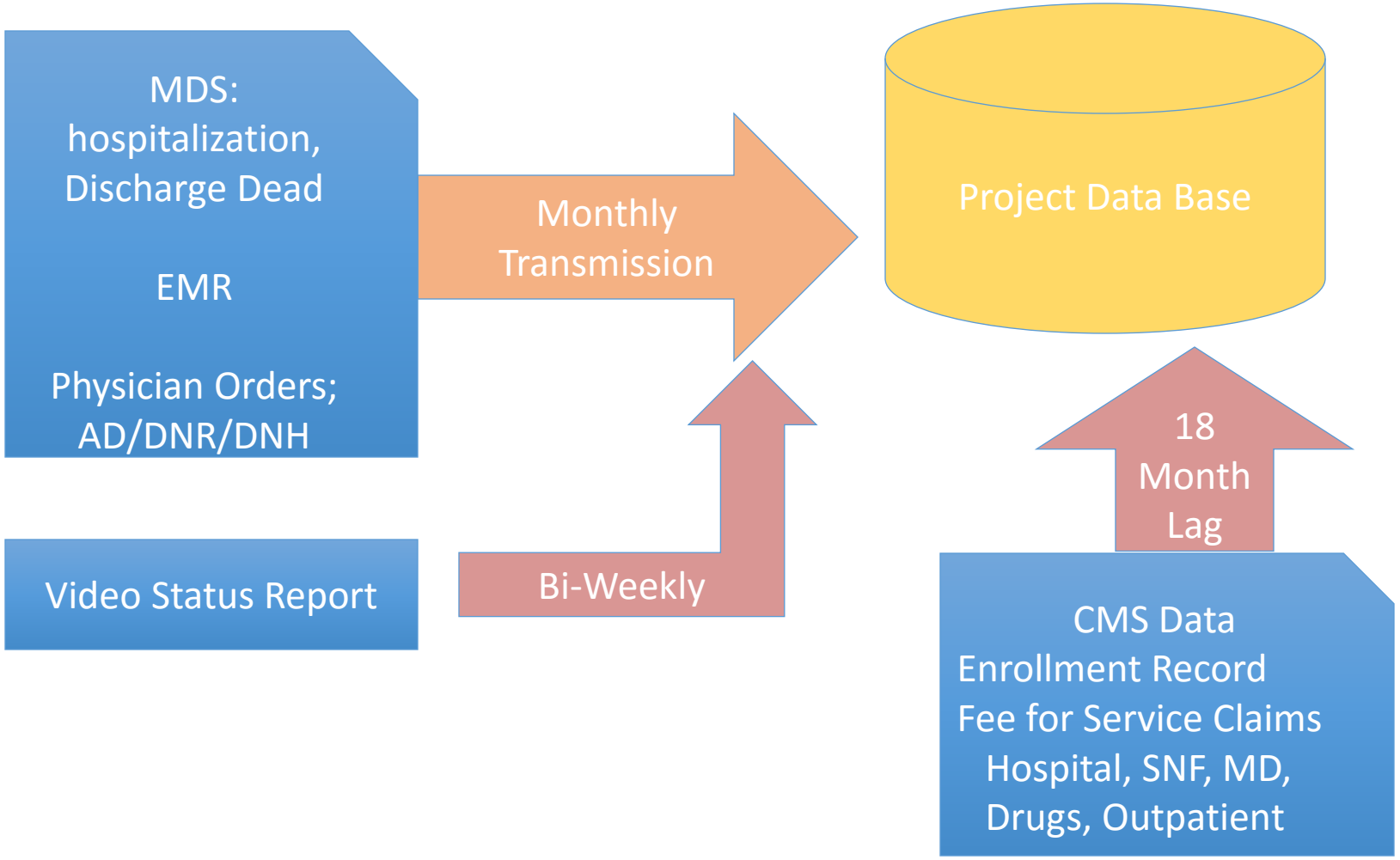
Training Toolkit

Table of Contents

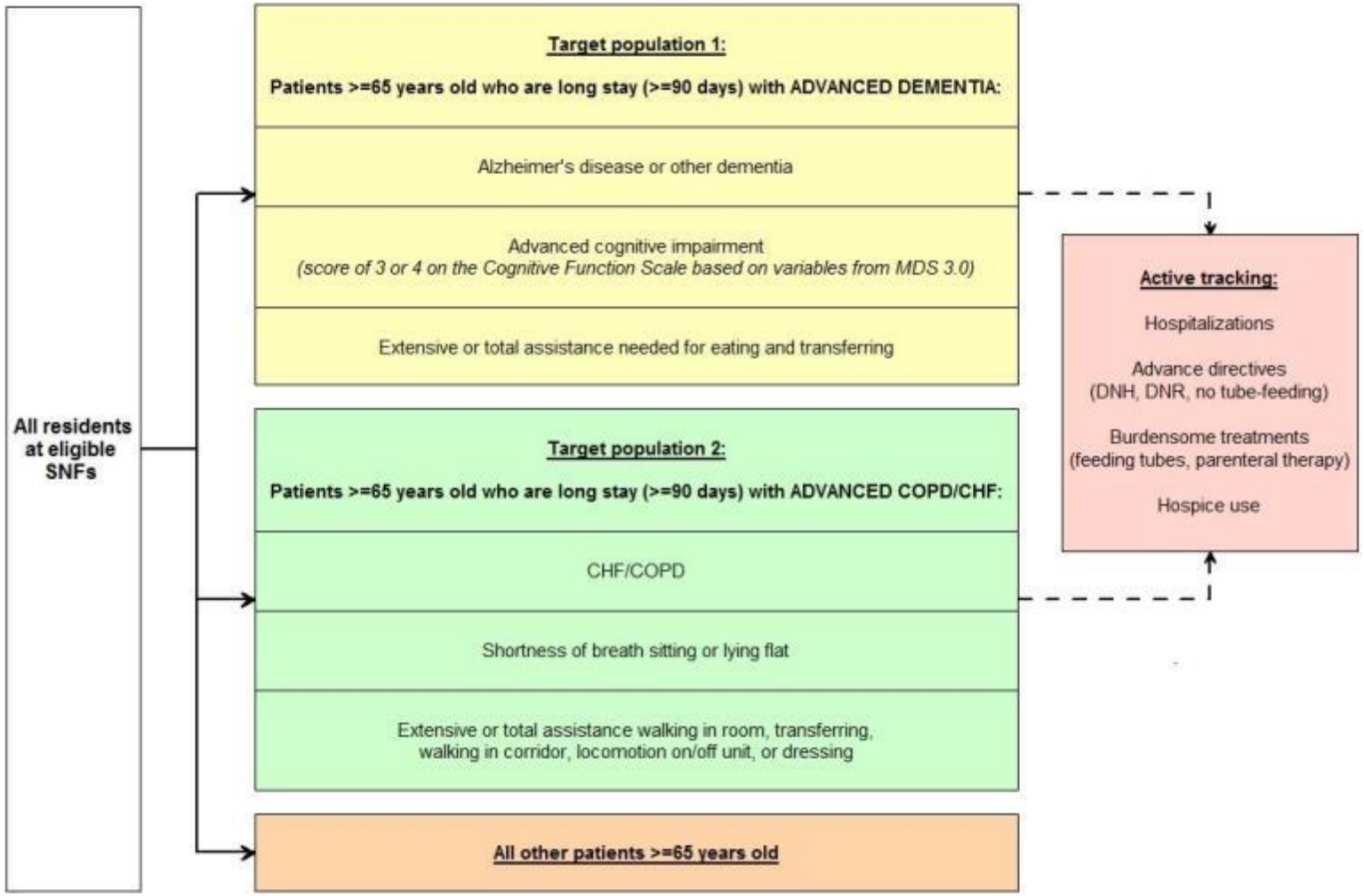
PROVEN: Human Subjects

- Seek waiver of individual consent (HHS 45 CFR 46:116)
  - NH unit of random Assignment
  - Facility-wide intervention
  - Minimal risk, cannot be carried out without waiver, patients welfare not adversely affected by waiver
- DSMB appointed by NIA
- Data Use Agreements

PROVEN: Data Flow



Analysis plan: Patient Sub-groups



PROVEN points to consider

- Availability of detailed, uniform, longitudinal person-level clinical and functional data opens the way to many investigations otherwise not possible
- Observational data analyses are much more powerful than before, BUT:
- Real-time data tracking under cluster RCTs is truly revolutionary

PROVEN Investigators & Collaborators

- Principal Investigators
  - Vince Mor, PhD
  - Susan L Mitchell MD, MPH
  - Angelo Volandes MD, MPH
- Partners
  - Barbara Yody (Genesis)
  - Sherry Johnson (Pruitt)
- Co-Investigators
  - Constantine Gatsonis PhD
  - Roee Gutman PhD
  - Pedro Gozalo PhD
  - Joan Teno MD
- Statistical Consultant
  - Allan Donner PhD
- NIH
  - Marcel Salive (NIA)
  - Jeri Miller (NINR)

Nuts & Bolts of applying for Pragmatic trial

- Funding announcements
  - RFA vs investigator-initiated?
  - Examine the review criteria closely
- Collaborations
  - Inter-disciplinary Research team
  - Practices and health systems
- Understanding your intervention
- Need for bridging/preliminary data
- Presenting it all within the page limit

Active Funding Announcements

NOTE: must apply to clinical trial Funding Opportunity Announcement (NOT-OD-16-147)

- Planning Grants for Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Prevention and Care (R34) NIDDK
- Pilot Effectiveness Trials for Treatment, Preventive and Services Interventions (R34) NIMH
- Encouraging Appropriate Care Using Behavioral Economics through Electronic Health Records (R21/R33) NIA
- Pragmatic Clinical Studies to Evaluate Patient-Centered Outcomes-PCORI

Encouraging Appropriate Care Using Behavioral Economics … **expanded review criteria**

APPROACH

- Is there a unifying and testable hypothesis that transcends both R21 and R33 phases?
- Does the application provide clear milestones for the R21 phase and related scientific goals for the R33 phase? Are those milestones conducive to accomplishing the study aims?
- Are the goals of the R33 phase based, in part, on findings collected during the R21 phase?
- Did the PDs/PIs establish an appropriate partnership with health care provider (e.g., primary care physicians, specialists, HMOs, etc) and document commitment of the organization to the project?
- Will the PDs/PIs be able to access EHR system to modify and implement pilot interventions using behavioral economics principles - e.g. is there an appropriate letter of support?
- Did the PDs/PIs provide adequate power calculations and adequate justification?
- Did the PI operationalize definitions and objective measures of the intervention - i.e., did the PDs/PIs cite evidence base to support the hypothesized mechanism of action of behavioral economics principle can be manipulated and implemented in EHR?
- Did the applicant assess and justify adequacy and finalize clinically-relevant outcome measures?
- Will the R21 phase produce preliminary data for R33 administrative review showing feasibility - i.e. can the PD/PI show he/she make changes to the EHR system and conduct an intervention?

Further Information

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