Partnering With Stakeholders to Conduct Embedded A vs. B Trials: **Keys to Success**

Stephen Friedhoff, MD
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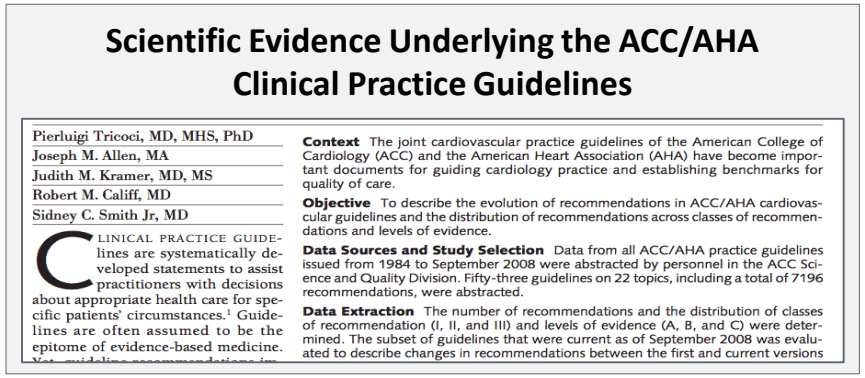
How Often Do We Know What to Do for the Consumer?

Cardiovascular Treatment Guidelines



Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for specific patients' circumstances.[1] Guidelines are often assumed to be the epitome of evidence-based medicine.

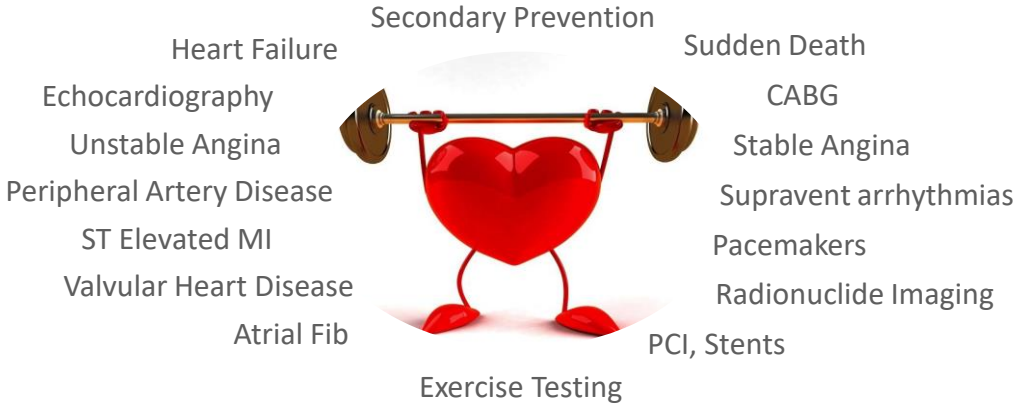
Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

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.

Data Extraction The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined. The subset of guidelines that were current as of September 2008 was evaluated to describe changes in recommendations between the first and current versions

JAMA. 2009;301(8):831-841



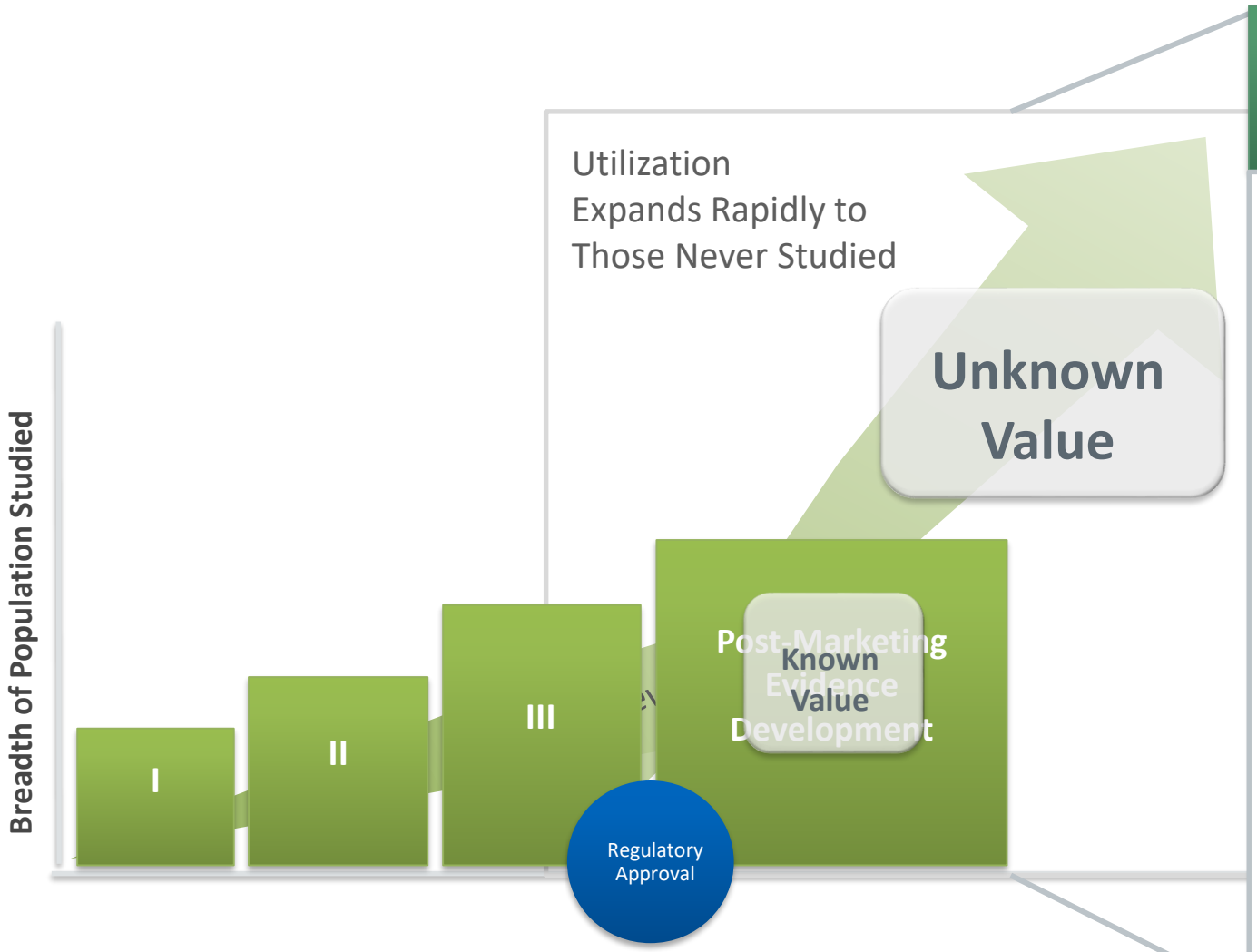
16 High impact cardiovascular guidelines used to power healthcare decisions by payers, healthcare providers and consumers

2,711 Recommendations within these guidelines

11% Were based upon enough evidence to warrant the recommendation. The vast majority were based upon a single trial and expert opinion

Current System Leaves Us with a Lack of Clarity

Utilization versus Evidence



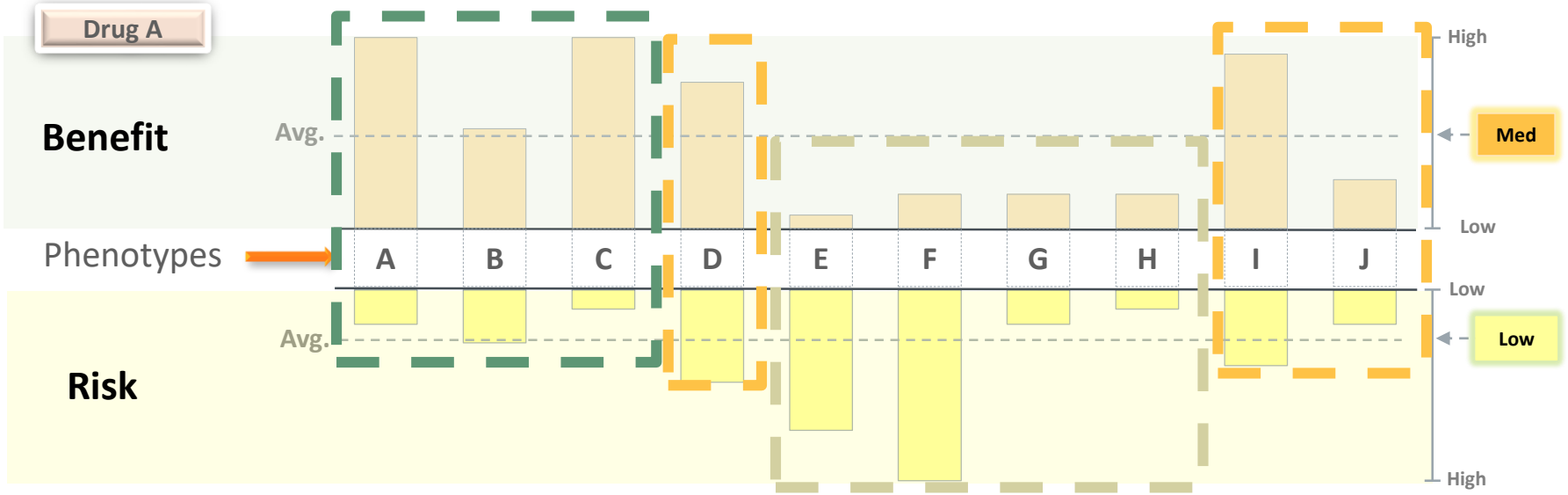
Variations in those using the product versus those that were studied in the trials

- ✓ Differing age groups (elderly, pediatrics)
- ✓ Race, ethnicity & gender variances
- ✓ Unstudied co-morbid conditions
- ✓ Differing concomitant drugs (including OTC)
- ✓ Lifestyle variances including smoking, dietary habits
- ✓ Differences in disease severity
- ✓ Varying levels of compliance

Current system tells us *if* a product works or *if* a product is safe, just not in *whom*

Healthcare Decisions are based upon
Benefit versus Risk+Cost

or

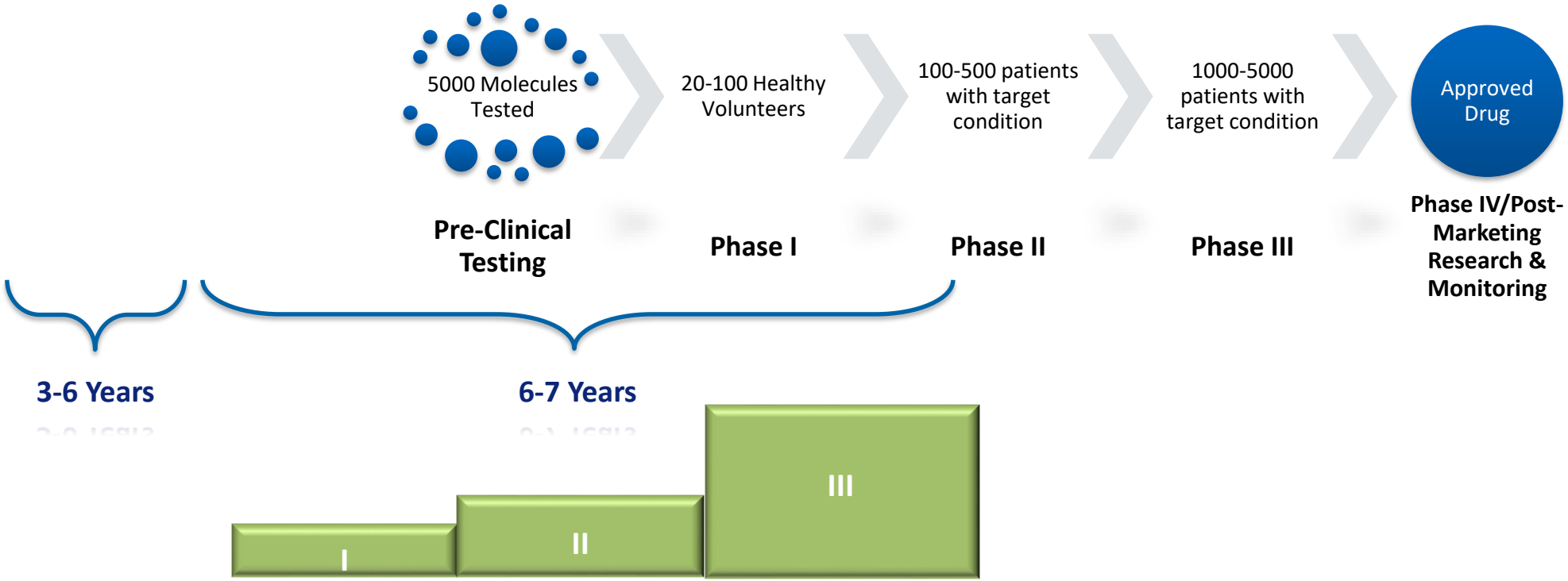


Our opportunity lies in leveraging our unique assets to derive this valuable insight better and faster than anyone else!

Current Technology Development Process

Its too slow, to expense and is relevant to too few

Under the current drug development & approval process it generally takes 10 years and more than $2B to generate evidence on 7,000-10,000 patients

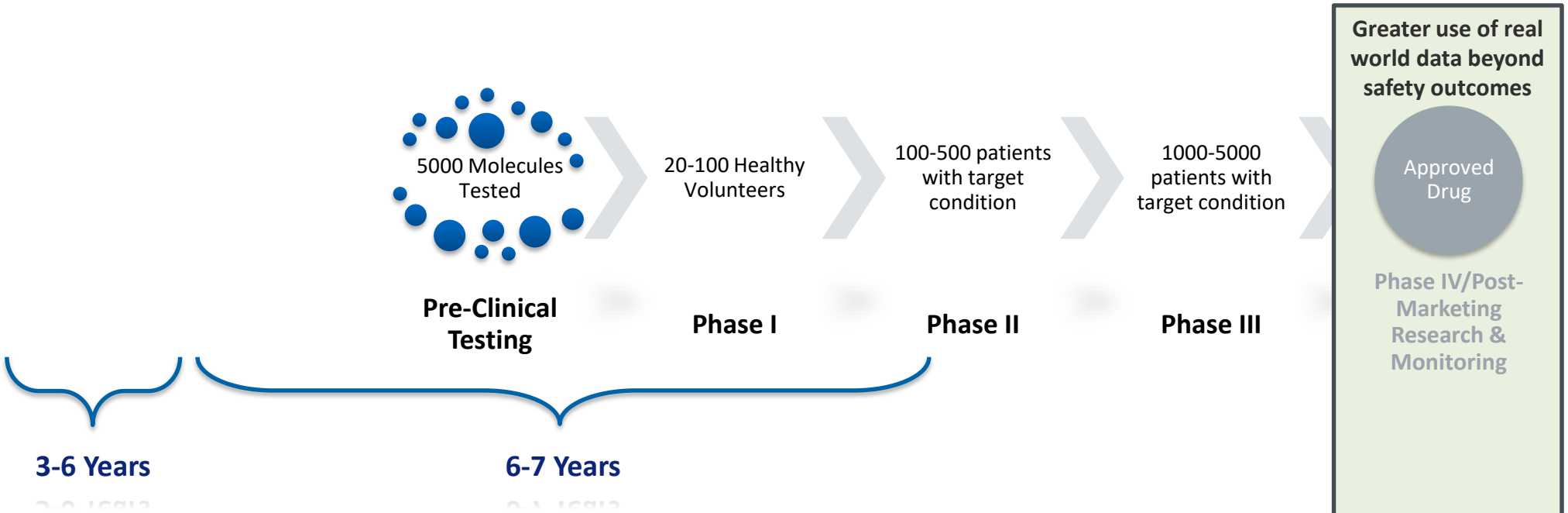


Leveraging Real-World Data to Close the Gap

A Step Forward

Evolutionary

Leverages existing and evolving real world evidence development infrastructure and evolves beyond safety to include effectiveness



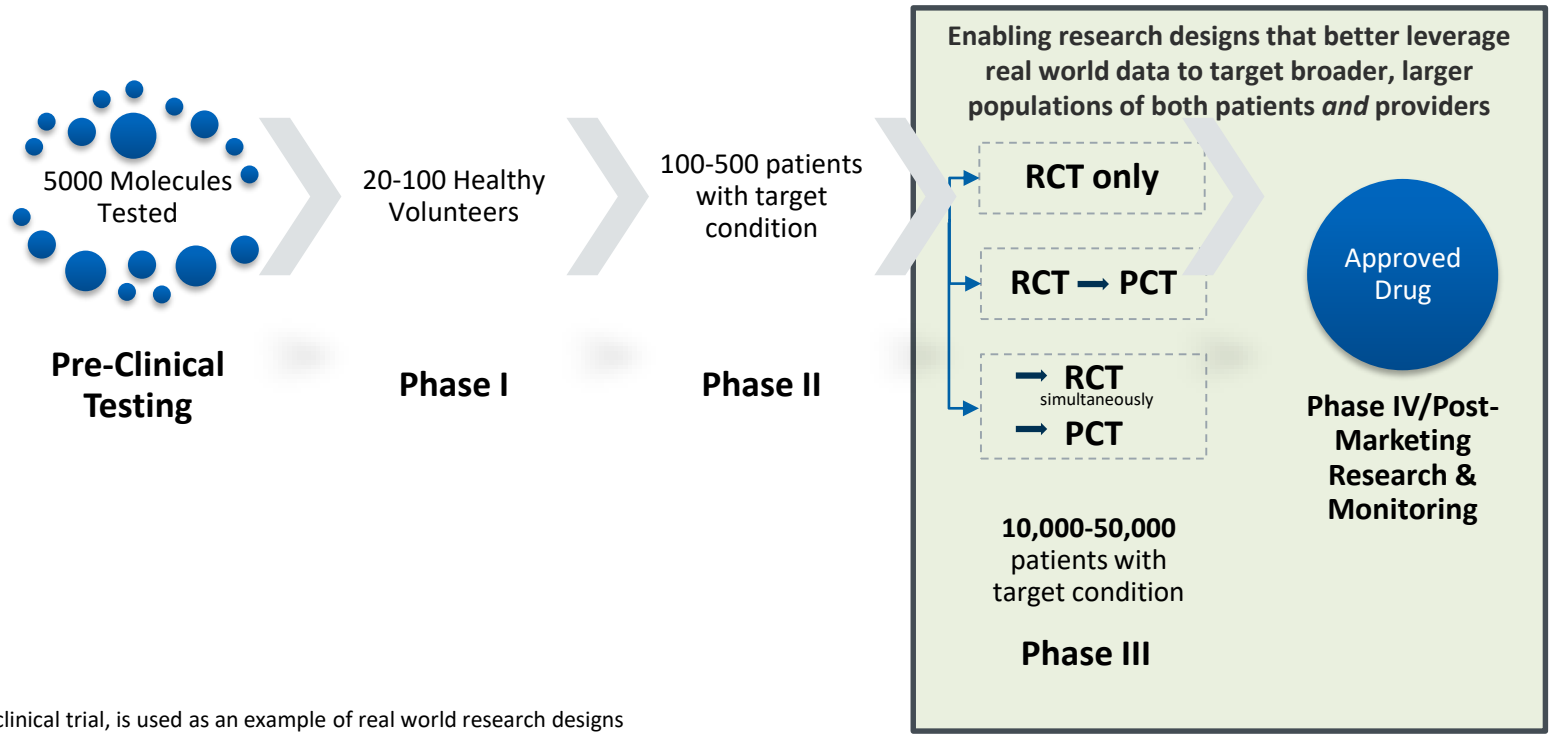
Timing is Still a Major Challenge

Future Drug Approval Process

Blending Traditional Trials with Late Phase Approaches

Revolutionary

Utilizes a “conditional approval” model to rapidly generate real world clinical, economic and humanistic results relevant to a larger population that are available at the point of final approval. Utilizes an infrastructure that collects most (if not all) needed data as a matter of routine clinical care.



- PCT, or pragmatic clinical trial, is used as an example of real world research designs
- RCT = randomized clinical trial

Rapidly Evolving Landscape

National Frameworks for Evidence Generation

IMPACT-AF

IMplementation of a randomized controlled trial to im**P**rove treatment with oral **A**nti**C**oagulan**T**s in patients with **A**trial **F**ibrillation

Direct mailer to health plan members and providers with Afib at high risk for stroke and no oral anticoagulant treatment

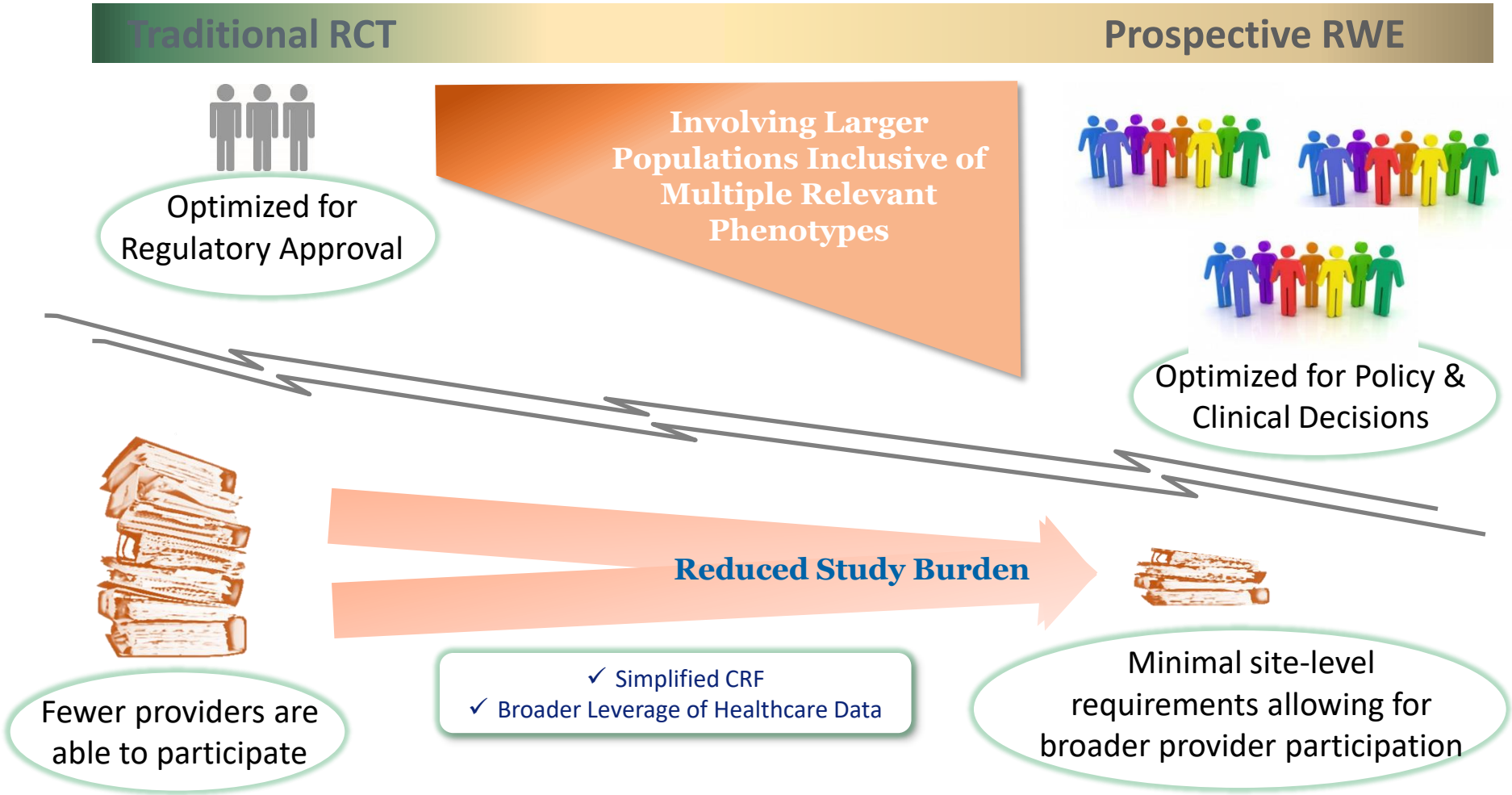
ADAPTABLE

Aspirin **D**osing: **A** **P**atient-centric **T**rial **A**ssessing **B**enefits and **L**ong-Term **E**ffectiveness

HealthCore has enrolled 238 members with additional outreach waves planned

Integrated Data Environment for PCTs

Reducing study burden on providers, increasing study opportunities



Late Phase Research

Examples: Pragmatic Clinical Trials

V-Go Diabetes Device

- Compare use of V-Go device in Adult T2 Diabetes patients needing insulin therapy to standard care
- Limited use of insulin in T2 DM patients and difficult to control population

Implication

Greater HgA1C reduction and less insulin used in V-Go patients

Cost saving in patient using V-Go versus standard care

AIRWISE Study

- Triple Therapy versus Dual Therapy evidence gap in COPD treatment guidelines (GOLD)
- New entry in market of single inhaler containing triple therapy

Implication

Provide needed evidence to assess value of triple or dual therapy in this high cost, at risk population

Address relevant and clinical health plan questions in COPD

Safety and Epidemiology Research

Example: Evidence-based research in opioid pain management

Opioid Risk Evaluation and Mitigation Strategy (REMS)

- Assess impact of REMS on serious adverse outcomes from the inappropriate prescription, misuse, and abuse of extended release (ER)/long-acting (LA) opioids
- REMS is effective in promoting receipt of the Medication Guide by patients using ER/LA opioids

Outcome

HealthCore continues to work with the ER/LA opioid manufacturers in compliance with the FDA in designing new studies to assess the impact of the ER/LA Opioid REMS by measuring changes in prescribing practices and patient outcomes

Opioid doctor/pharmacy shopping

- Doctor/pharmacy shopping as a measure of opioid misuse, abuse, addiction, and diversion
- Severe shopping (>4 prescribers; >2 pharmacies) behaviors are more likely suggestive of misuse, diversion, abuse, and/or addiction behaviors

Outcome

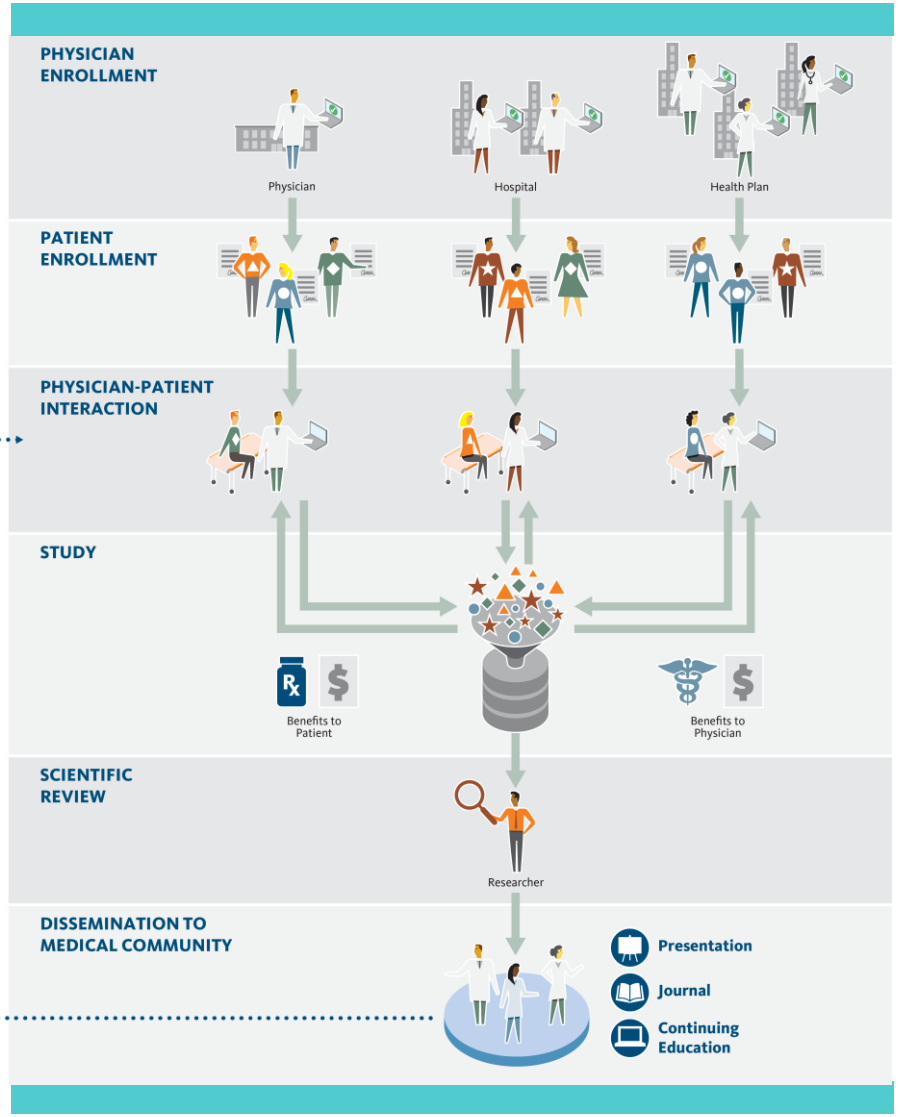
In collaboration with the ER/LA opioid manufacturers, HealthCore is evaluating whether different ways of assessing opioid misuse, abuse, addiction and diversion, such as direct patient perspectives, confirm the correlation between doctor/pharmacy shopping and aberrant use

HealthCore is creating an ecosystem of collaboration and discovery

Integrated Research Network® (IRN®)

- Connected network of health plans, care providers, integrated delivery systems, and patients
- Enables the rapid generation, implementation, and dissemination of real-world evidence

Any care provider can participate.



IRN Provider Survey Executive Summary

Reaction to the IRN description

- The IRN concept and value props were easily understood, and providers see a research network like the IRN as filling a gap in current patient care
- **The vast majority of providers (86%) are interested joining in the IRN**.
- Providers anticipate knowledge and information gained from the IRN would lead to **effective decision making** and **higher patient satisfaction**.
- Providers are most concerned about the **time commitment** necessary to participate in the IRN.

Value Proposition / Benefits of IRN

- Most valued benefits include **contributing to RWE, improving clinical decision making**, **ease of participation** and **reimbursement for participation**.
- Publication experience and CME opportunities were mixed – some providers ranked these as important and some ranked near the bottom
- Feedback loop of RWE and insights coming out of the IRN was also seen as a critical benefit (will look to tap into NERI's digital strategy expertise here)

Online Portal / Social Media

- Physicians desire **research study opportunity information** (future and current) and **access to publications** and **feedback from past studies**.
- Most believe that **interactive/social media features are not necessary for a provider portal**, but if available, over half indicate they would use the feature.

Embedded Pragmatic Clinical Trials of A vs. B Therapeutic Interventions

Partnering with Stakeholders: Keys to Success

May 16, 2018
Bethesda, MD

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HCA®

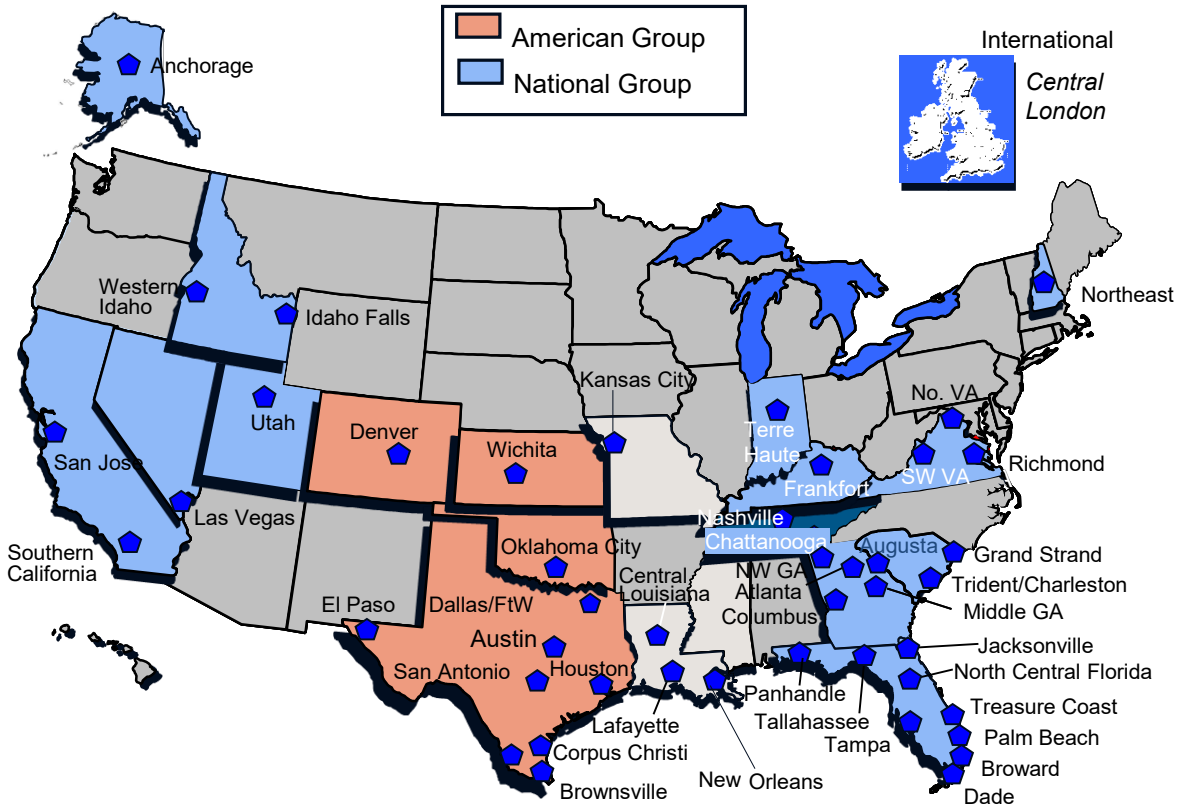
HCA Healthcare

28 million patient encounters annually

Approximately 5% of major hospital services in U.S.:

- Admissions > 1.6 million
- Patient Days > 7.6 million
- Deliveries > 0.25 million
- Total Surgeries > 1.3 million
- ED Visits > 8.5 million

- 177 hospitals and > 120 freestanding surgery centers located in 20 states and London
- Hospitals range from complex tertiary referral and academic medical centers to urban and suburban community medical centers
- ~ 233,000 employees, including ~ 79,000 nurses and 30,000 allied health professionals
- > 37,000 active physicians, including > 3,500 employed physicians and advanced practitioners
- More than 40,000 licensed beds



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HCA Clinical Services Group (CSG)

PURPOSE

Drive excellent care at-scale

VISION

HCA will be the recognized leader in care delivery achieving world-class outcomes

Strategic Framework

DRIVE SUPERIOR COMPETENCIES & CAPABILITIES

DRIVE EXCELLENT CLINICAL OPERATIONS

LEVERAGE DATA & TECHNOLOGY

ASSURE CORPORATE RESPONSIBILITY & ORGANIZATIONAL ADVOCACY

HCA®

Roles of Research at HCA

- Core to mission (“care and improvement of human life”)
  - Important activity within domain of corporate responsibility and advocacy
  - Extension of commitment to “evidence-based medicine”
- Core to being a learning health system (And to GME program requirements)
- Formal evaluation needs to be part of credible performance improvement
- Key strategy for physician recruitment and engagement
- Market differentiator
- Reputation builder
- Platform for synergistic partnership . . .

REDUCE MRSA

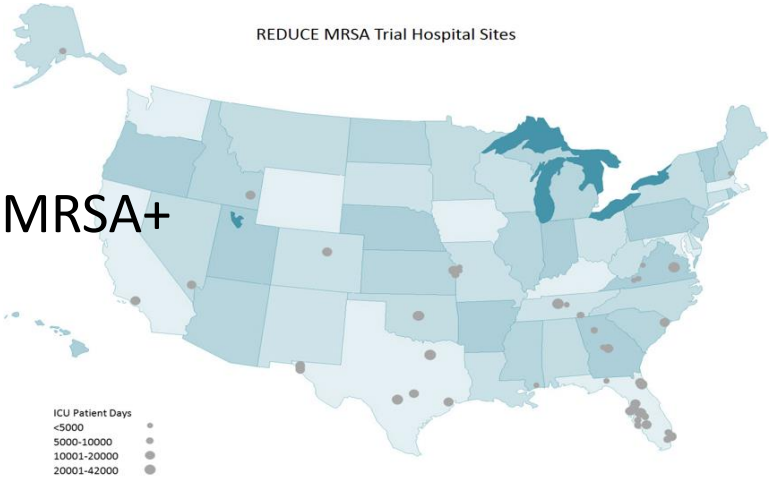
Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin Resistant *Staphylococcus Aureus*

Research Question:

- Among competing protocols (in equipoise), which is most effective at reducing MRSA and Bloodstream Infections among ICU patients?

Trial Design: Pragmatic, 3-Arm, Comparative-Effectiveness Trial, Cluster-Randomized by hospital

- **43 HCA hospitals with 74 adult critical care units**
  - Routine Care: Screen all and isolate if MRSA+
  - Targeted Decolonization*: Screen all, isolate and decolonize if MRSA+
  - Universal Decolonization: Decolonize all



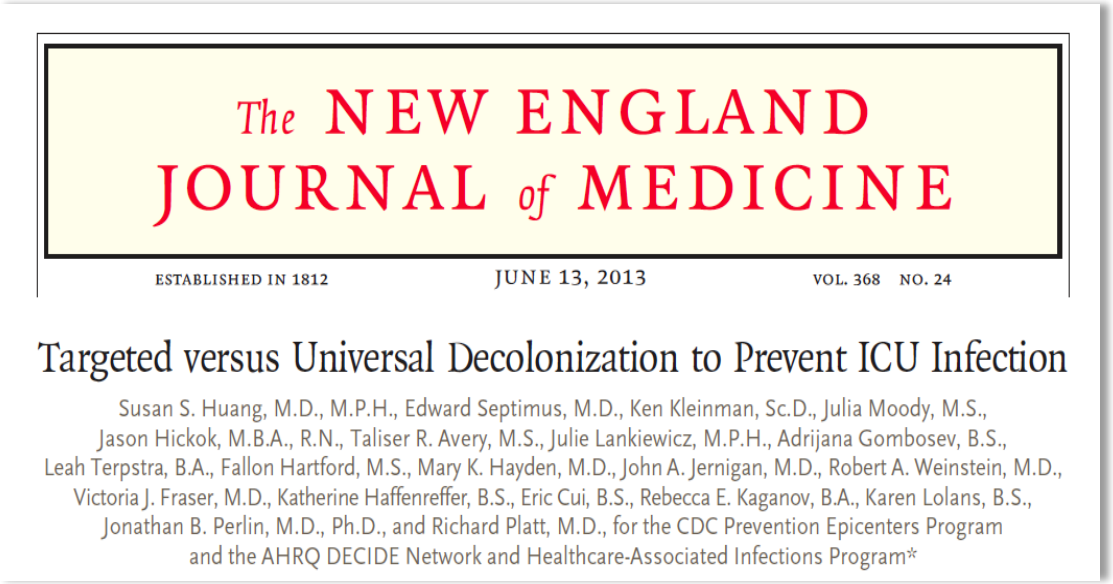
18 month intervention: April 2009 – September 2011

- 74,256 patients
- 283,000 ICU patient days

REDUCE MRSA: Study Findings

Universal Decolonization Reduces All Blood Stream Infections (BSIs) by 44% and MRSA isolates by 37%

- **For every 99 patients decolonized, 1 BSI was avoided**
  - **Set a new standard for reducing BSIs in ICUs**



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Targeted versus Universal Decolonization to Prevent ICU Infection

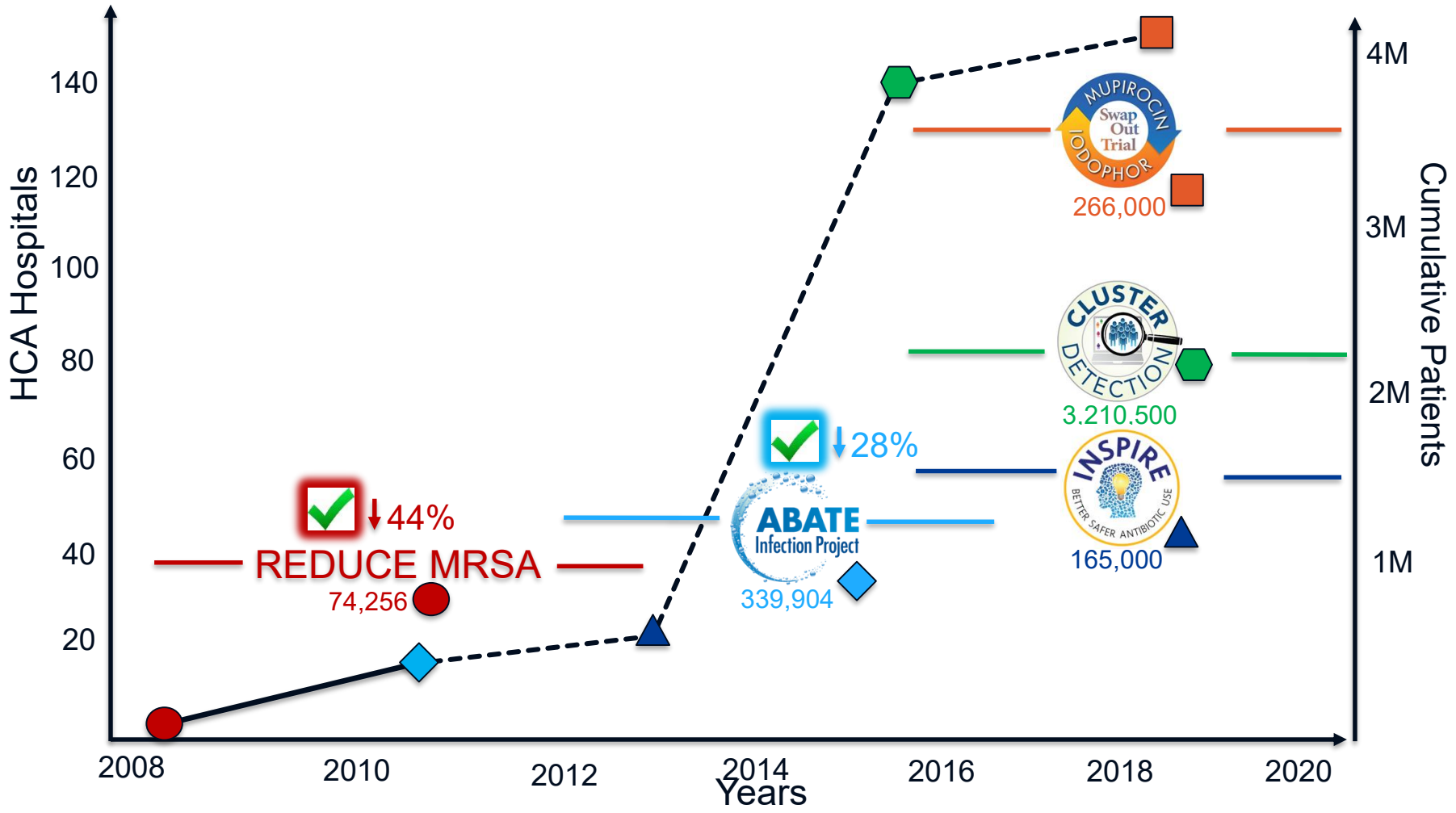
Susan S. Huang, M.D., M.P.H., Edward Septimus, M.D., Ken Kleinman, Sc.D., Julia Moody, M.S., Jason Hickok, M.B.A., R.N., Taliser R. Avery, M.S., Julie Lankiewicz, M.P.H., Adrijana Gombosev, B.S., Leah Terpstra, B.A., Fallon Hartford, M.S., Mary K. Hayden, M.D., John A. Jernigan, M.D., Robert A. Weinstein, M.D., Victoria J. Fraser, M.D., Katherine Haffenreffer, B.S., Eric Cui, B.S., Rebecca E. Kaganov, B.A., Karen Lolans, B.S., Jonathan B. Perlin, M.D., Ph.D., and Richard Platt, M.D., for the CDC Prevention Epicenters Program and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

RESEARCH PARTNERS

- Agency for Healthcare Research and Quality
- CDC & Prevention Epicenters
- Harvard Pilgrim Health Care Institute / Harvard Medical School
- Hospital Corporation of America
- Rush University
- University of California Irvine

HCA Partnership Cluster Randomized Trials

Advancing medical knowledge, one pragmatic study at a time



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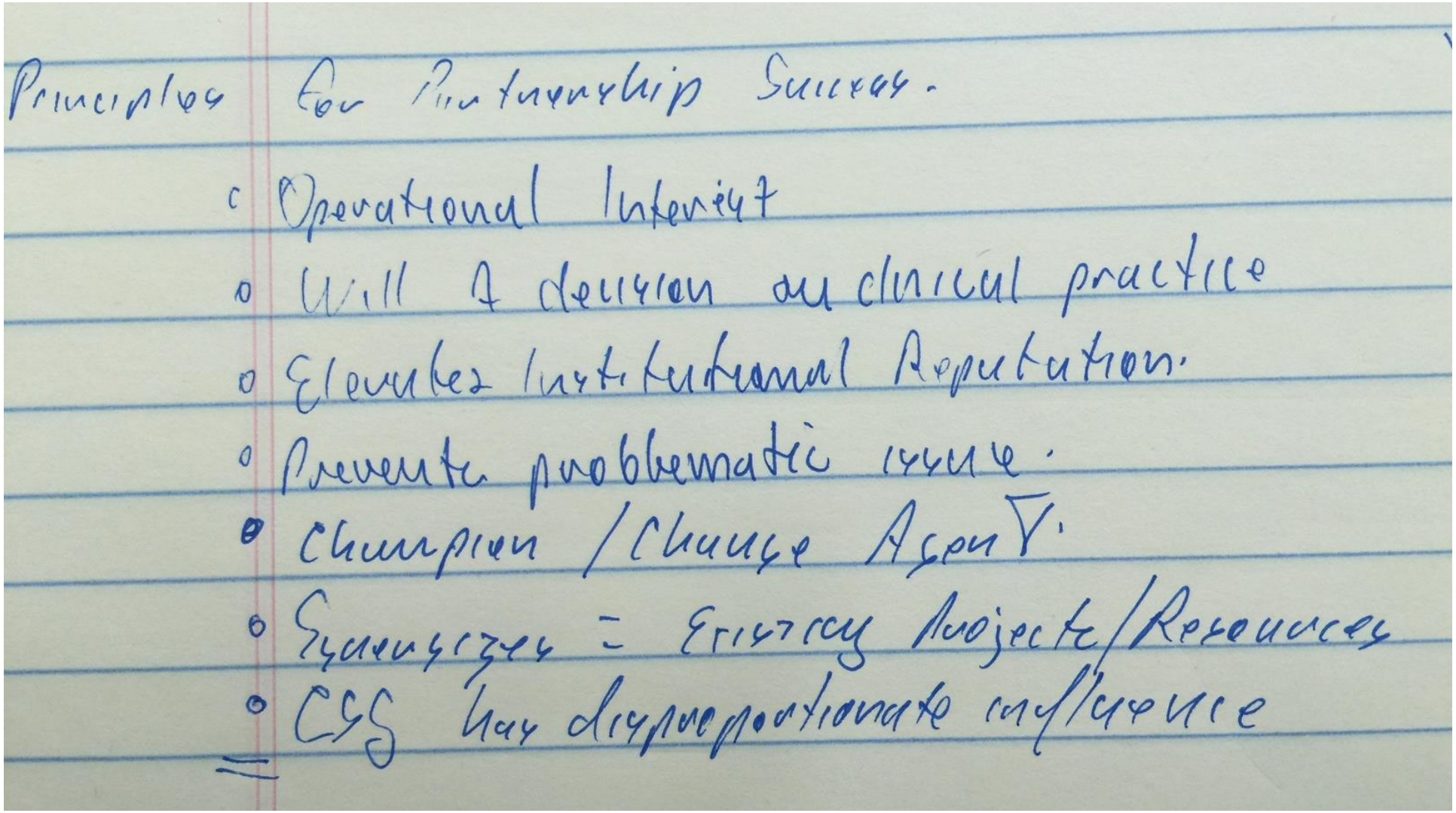
Deconstructing Partnership: What Predicts Success . . .



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Health System Research Collaboration:

Principles of Partnership . . .

1. An empowered champion must provide enterprise leadership
2. Question has to be operationally or strategically important, but not adverse to operations
3. Activity has to be largely transparent or similar to normal workflow
4. Questions must be inserted into operations cadence;
   schedule cannot be driven by research timing
5. Question must be clinically important
   (clarifying alternatives, and providing an adoptable solution)
6. Participation must provide benefit for each collaborating organization
7. Intellectual property is equitably shared, and sharing is determined *a priori*
8. Data security is paramount (and data at-rest are more secure)
9. Data systems should be architected for learning health care
10. Partnership has to be symmetric (”win-win”), feel equitable, and be broadly perceived as such

Pragmatic Trials: Lessons Learned

Positive Lessons:

- Stronger Learning Healthcare System from academic-public-private partnership
- Pragmatic research feasible in operationally sophisticated healthcare system
- Successful collaboration between experts on research design and real-world implementation
- Sophistication in data management is stretched thru partnership
- Ability to reinforce mission and define national practice

Challenges:

- Intangible “costs” are substantial (personnel time, IT, distraction, supply chain, competing opportunity)
- Defining relationships can be complex, lengthy, and costly (legal costs).
- Need to holding the line on competing interventions
- Operational and research timelines may fall out of synch
- Communication between and within organizations with complex structures and differing priorities

HCA®

Health System Research Collaboration:

Principles of Partnership also determine bandwidth . . .

1. An empowered champion must provide enterprise leadership
2. Question has to be operationally or strategically important, but not adverse to operations
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Medicare Coverage & Evidence Development

Joseph Chin
05/16/2018

Disclaimers

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This presentation was prepared as a service to the public and is not intended to grant rights or impose obligations. This fact sheet may contain references or links to statutes, regulations, or other policy materials. The information provided is only intended to be a general summary. It is not intended to take the place of either the written law or regulations. We encourage readers to review the specific statutes, regulations, and other interpretive materials for a full and accurate statement of their contents.

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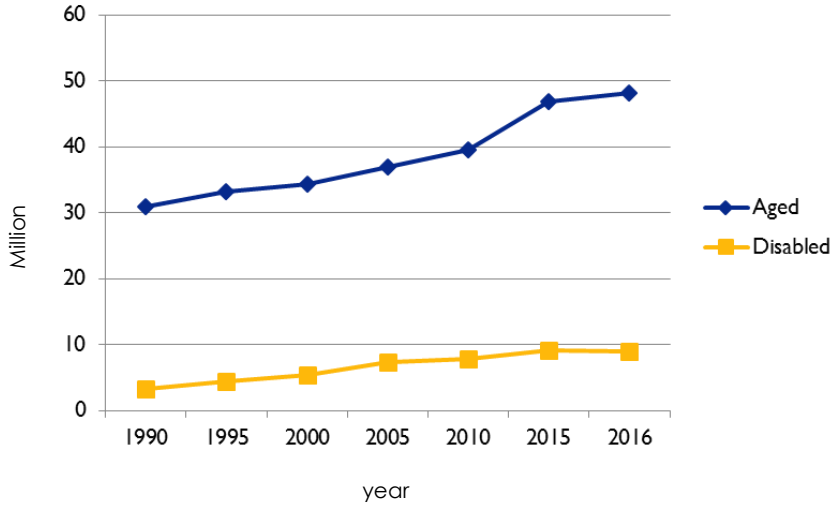
Medicare Construct

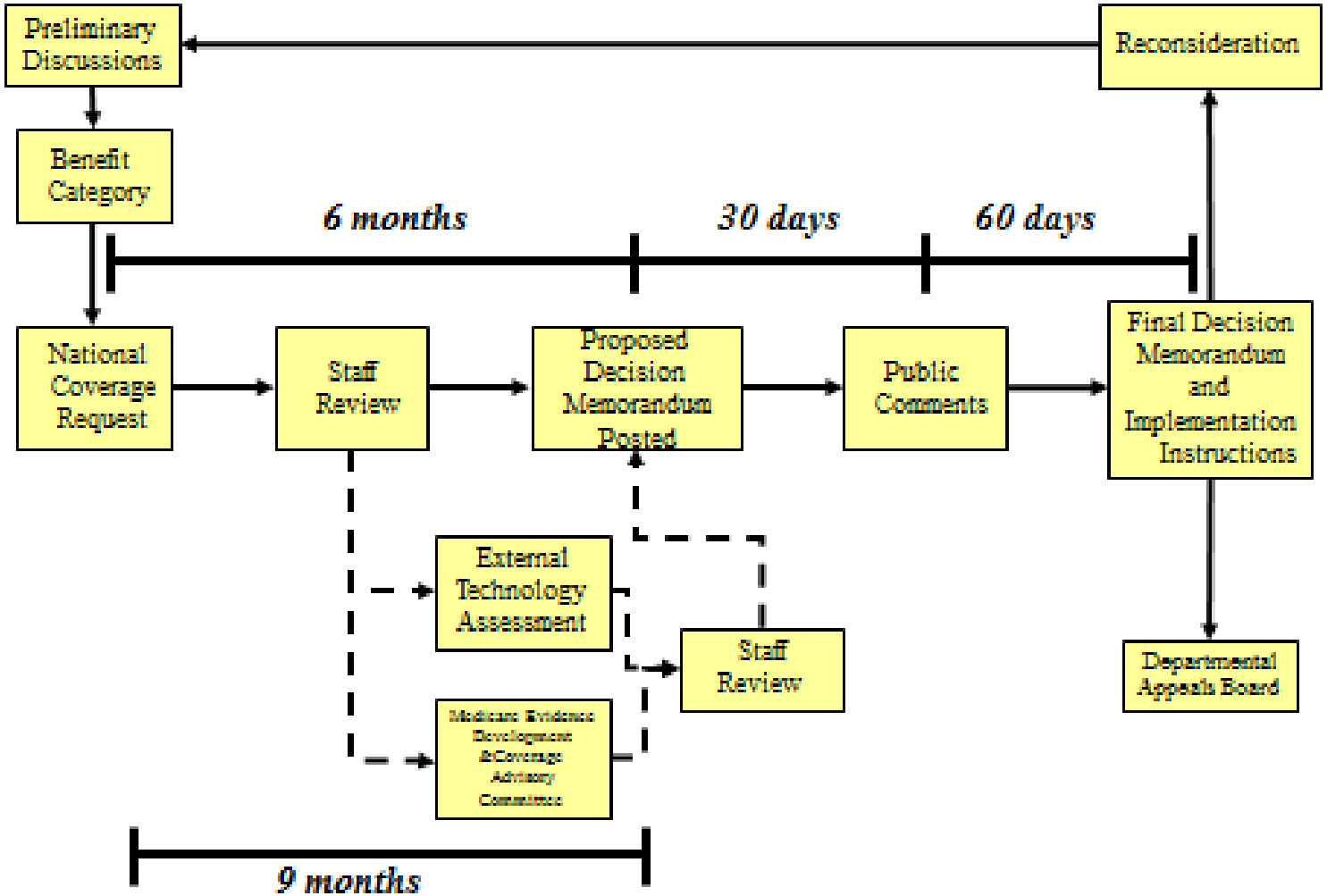
- Established by the Social Security Act of 1965, Title XVIII
  - §1862(a)(1)(A) reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member
  - (E) in the case of research conducted pursuant to §1142, which is not reasonable and necessary
- Defined benefit program
  - Beneficiaries
    - Age ≥ 65 years
    - Disabled individuals
    - End stage renal disease (557 million)
  - Providers
  - Settings



Evidence-based Medicare Coverage

- Coverage determinations address whether the evidence is sufficient to conclude that the item (drug or device) or service improves clinically meaningful health outcomes for the Medicare population
- Considers the quality, strength and totality of evidence
- Focuses on important patient centered outcomes

MEDICARE NATIONAL COVERAGE PROCESS



Medicare Beneficiaries in Clinical Studies

- Initial studies on new technologies may not include many older adults ≥ 65 years of age for several reasons including:
  - Heterogeneity – may have multiple comorbidities and/or be taking multiple medications
  - Non-adherence - may have difficulty following protocols and/or making all study follow-up visits
  - Other considerations – measurement issues, cognitive function

Study Endpoints and Eligibility Criteria

- Important to determine the strength and generalizability of published evidence to the Medicare population
- May assist in establishing parameters of coverage with evidence development (CED)

Inclusion Criteria in National Coverage Determinations

- Patients eligibility criteria in national coverage determinations (NCDs) may reflect inclusion criteria of the studies forming the evidence base for the item or services, for example:
  - Implantable cardioverter defibrillators (ICDs)

Trial	Covered Indication
Multicenter Automatic Defibrillator Trial (Moss, 1996)	Documented prior myocardial infarction, left ventricular ejection fraction ≤ 0.35, and inducible, sustained ventricular tachycardia or fibrillation at electrophysiology study.
Multicenter Automatic Defibrillator Trial II (Moss, 2002)	Documented prior myocardial infarction and a measured left ventricular ejection fraction ≤ 0.30.
Sudden Cardiac Death in Heart Failure Trial (Bardy, 2005)	Nonischemic dilated cardiomyopathy > 3 months, NYHA Class II or III heart failure, and measured LVEF ≤ 35%.

Study Exclusion Criteria

- Older adults may be excluded from initial studies assessing efficacy.
- Patients with end stage renal disease (ESRD) are often excluded.

Coverage with Evidence Development (CED)

- Coverage in the context of approved clinical studies or with the collection of additional clinical data
- Allows for positive coverage when evidence is insufficient for a more favorable decision.
  - Evidence gaps may be due to low number of beneficiaries in clinical studies, lack of meaningful health outcomes, limited generalizability, inconsistency of study findings.
- May involve randomized controlled trials, observational studies and/or registries
    - Specific interventions,
    - benefits and harms,
    - health outcomes

Other Clinical Studies under Medicare

1. Investigational Device Exemptions (IDE) Studies
   - Regulation at 42 CFR 405.201
   - New centralized process in 2015
2. Clinical Trial Policy
   - Routine costs in clinical trials funded by certain federal agencies
   - National Coverage Determination (NCD)

     Pub 100-3, Section 310.1

THANK YOU.