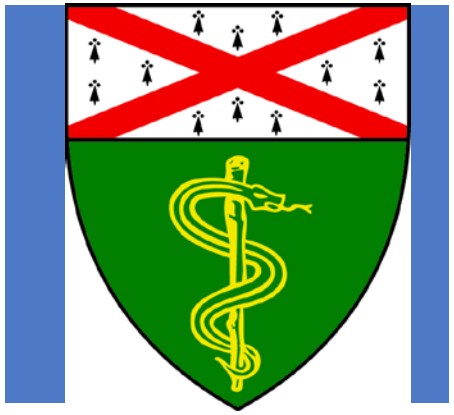
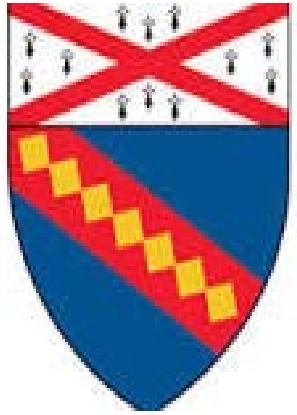
Inclusion/exclusion criteria and trial design



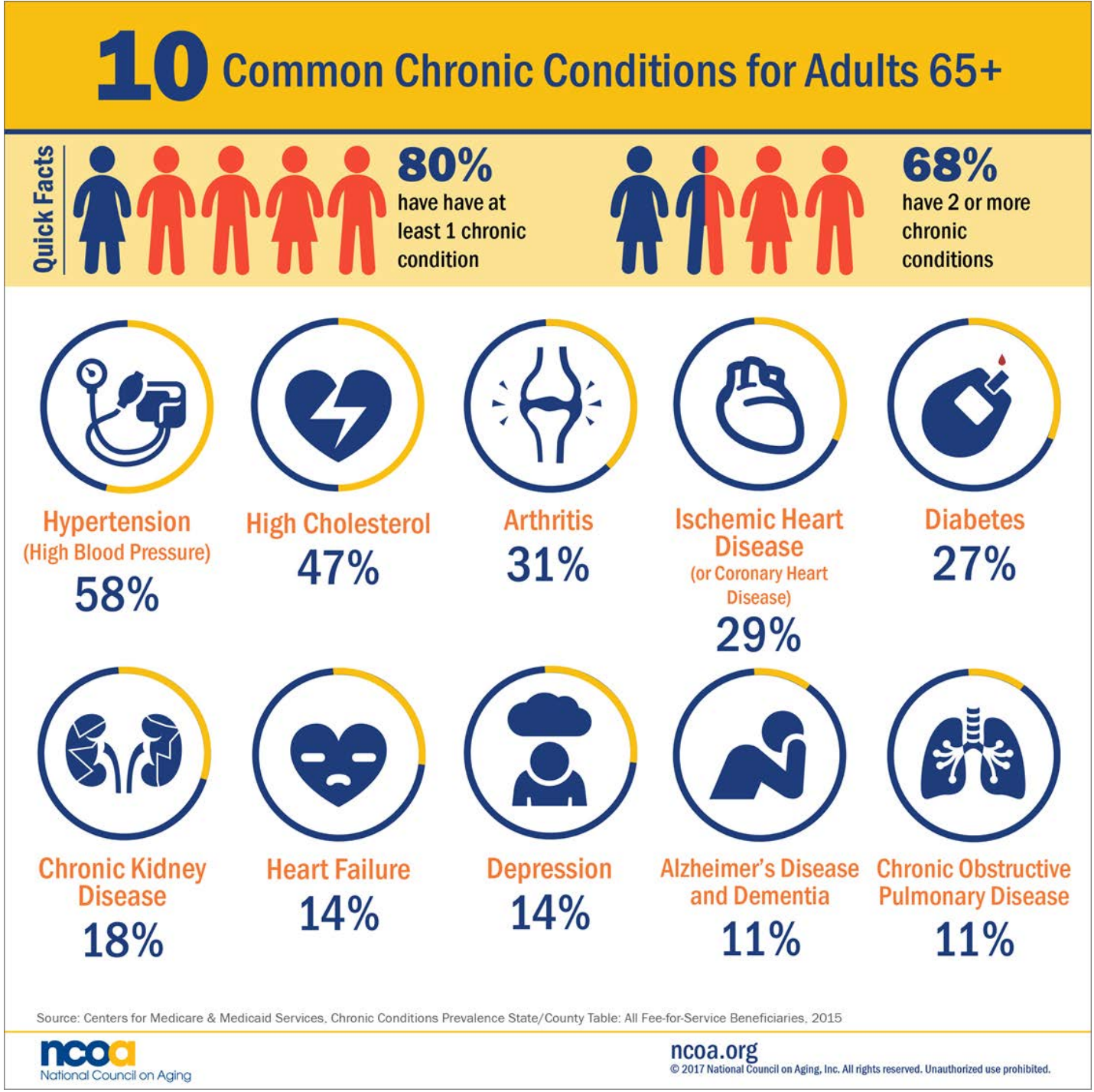
Heather Allore, PhD
Yale School of Medicine
Yale School of Public Health



30% of older adults in the US take ≥5 drugs[1]

Adverse drug reactions are:

- **Prevalent**: 4 hospitalizations /1000 person-years, [2]
- **Serious**: among top 10 common causes of death, [3]
- **Expensive**: annual costs between $30 billion to $180 billion.[4, 5]



Older Adults Under-Represented in Trials

- Medicare beneficiaries differ significantly from the clinical trial participants used to inform Medicare coverage decisions.
- The clinical trials rarely included outcome stratification by age, sex, and race. [6]

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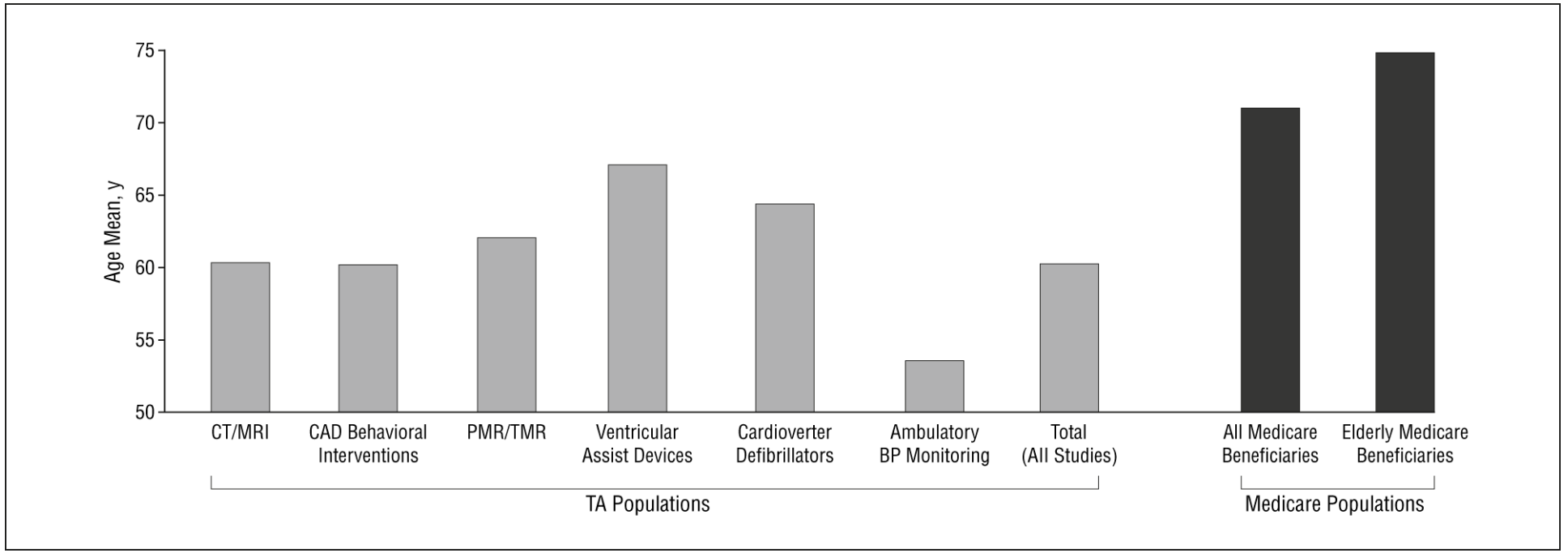
From: **Variations Between Clinical Trial Participants and Medicare Beneficiaries in Evidence Used for Medicare National Coverage Decisions**

Arch Intern Med. 2008;168(2):136-140. doi:10.1001/archinternmed.2007.56



Mean age in technology assessment (TA) study populations compared with Medicare beneficiary populations. BP indicates blood pressure; CAD, coronary artery disease; CT, computed tomography; MRI, magnetic resonance imaging; PMR, percutaneous myocardial revascularization; and TMR, transmyocardial revascularization.

Older Patients (Still) Left Out of Cancer Clinical Trials[7]

7. Abbasi J. Older Patients (Still) Left Out of Cancer Clinical Trials. *JAMA.* 2019;322(18):1751–1753.

Exclusion Criteria

- Exclusion criteria may be poorly justified age-related factors (comorbidities, concurrent medication etc.), even when they have little bearing on the treatment that is studied. [8]

What can be done?

- Require **strong justification** for exclusion criteria;
- Encourage **clinical trials specific to older adults** through targeted federal funding;
- **Publicize trends in the inclusion of older adults** in clinical trials to assess progress;[9]
- **Require direct evidence of benefit in making national coverage determinations of services for Medicare beneficiaries**, which would serve as a powerful incentive to enhance the participation of older persons in clinical trials.[6]

Design Should Produce Relevant Results

- Design trials to **produce relevant and generalizable results for older, comorbid adults**, by including patients clinicians care for in routine practice.
- Rather than reliance on traditional, parallel-group randomized controlled trials, consider **adaptive platform trial** designs that study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform based on a predefined decision algorithm. [10]

Adaptive Platform Trials

- Currently, most used in Phase II trials
- Randomized embedded multifactorial adaptive platform (REMAP) design are intended to be embedded in clinical practice to leverage efficiencies in trial execution and to provide continually updated randomized evidence on best practice within a learning health system. [11]
- Offer numerous advantages in both pharmaceutical and device development and comparative effectiveness settings, helping to bridge the knowledge translation gap between traditional RCTs and clinical practice. [10]

Outcomes

International Consortium for Health Outcomes Measurement proposed outcomes relevant to older adults[12]:

- Participation in decision making,
- Autonomy and control,
- Mood and emotional health, Loneliness and Isolation,
- Pain,
- Activities of daily living, Frailty,
- Time spent in hospital, Overall survival,
- Carer burden,
- Polypharmacy,
- Falls,
- Place of death mapped to a 3-tier value-based healthcare framework.

Challenges

- Pharmaceutical companies follow the design and analysis guidance of the FDA and are risk-adverse about including older high-risk adults.
- Disconnect in who covers costs:
  - Pharmaceutical companies cover drug development
  - Taxpayers and insurers cover the cost of adverse drug reactions
- FDA required outcomes are disconnected from priorities of older adults.
- Unknown whether drugs act similarly when taken with 2, 5, 10 or more drug

Summary

- If we continue to conduct traditional clinical trials excluding older adults, the greatest users of medications, then we will continue to:
  - Have unacceptably high level of adverse drug reactions
  - Have taxpayers & insurer cover increased costs from adverse drug reactions
  - Have uninformed clinical decision-making for older adults
  - Be unable to address outcomes that matter most to older adults.
- Using modern trial designs, where participants reflect the population with the disease, measuring relevant outcomes may address deficits.
- Publicize trends in the inclusion of older adults in clinical trials to assess progress in improving the generalizability of research

References

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