What Should Be the Framework for Older Adults and How Can We Achieve It? —A Clinical Trials Perspective

Roadmap to 2030 for New Drug Evaluation in Older Adults

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March 23rd, 2021

(20 mins)

The Food and Drug Administration is responsible for protecting the public health by **ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices**;

FDA is responsible for advancing the public health by helping to speed innovations that **make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.**

https://www.fda.gov/about-fda/what-we-do

Quadruple Aim

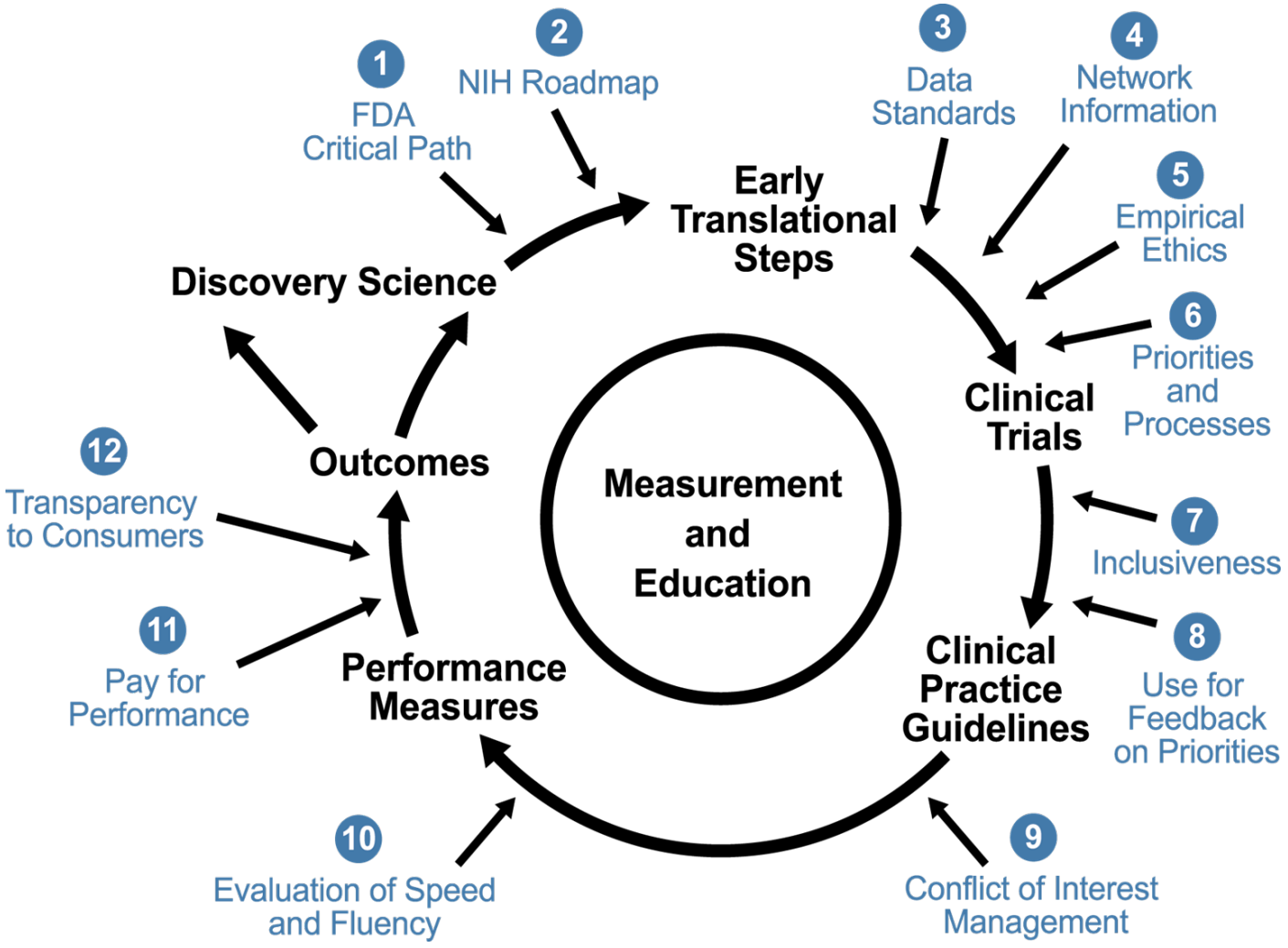
Lower costs	Better “Patient” Experience
Better Clinician Experience	**Better Clinical Outcomes**

HEALTH AFFAIRS VOL. 27, NO. 3: HEALTH REFORM REVISITED

Donald M. Berwick,, Thomas W. Nolan, John Whittingto

From Triple to Quadruple Aim: Care of the Patient Requires Care of the Provider Thomas Bodenheimer, MD1† and Christine Sinsky, MD2,3

Generating Evidence to Inform Decisions



What are we Trying to Achieve with a Framework?

- As people get older, they change with regard to biology, behavior and social interactions
- These changes are multi-dimensional and not binary, so arbitrary dichotomous measures are frustratingly inadequate to characterize the problem
- A large and growing proportion of prescription drugs and adverse drug events occur in older people, especially those with multiple diseases (and therefore multiple medications)
- Most experts agree that traditional drug development in younger research participants is unlikely to adequately inform prescribing in the aging population
- The general goal should be to ensure that drug labels and clinical practice guidelines are supported by high quality evidence for intended use in practice

Observations

- Age is not amenable to “binarization” or “dichotomania” (the difference between chronological age and biological manifestations of aging is being explored; e.g. telemore length, etc.)
- People of the same age with different comorbidities (type and number) face very different issues with health and with pharmacologic therapy
- As a continuum, older people are poorly represented in clinical trials
- Not enough basic pharmacology studies are being done
- Even when basic pharmacology is known we lack information about the many issues in the real world that affect benefit-risk
  - Polypharmacy and interactions
  - Risk related to effects of cognition and adherence
  - Risk related to physical issues (falls, accidents, etc.)
- In new drug development time is money—delays in time to approval for the few new drugs with benefits > risk cost a lot and may deny effective treatment to younger adults

Among the many lessons from the pandemic, we have learned that clinical trials with randomization are usually needed to draw valid causal inferences about treatment effects!

- Hydroxychloroquine
- Convalescent plasma
- Vitamin D
- …. Need I say more?

Clinical Trial Perspective

- **NIH Definition of a Clinical Trial**
  - A 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.
- A clinical trial requires an ecosystem
  - Sponsor
  - Investigators/health systems
  - Research participants
  - Regulators—federal and institutional

If we need clinical trials, what is holding us back?

- Randomization
  - The concept of randomization
  - The complex trade-off of protecting the vulnerable versus the need to have reliable knowledge about best treatment
- Inadequate support for integration of research and clinical practice

Randomization

- Both in the clinical and lay community there are significant concerns about randomization as a method
  - “guinea pigs”, etc.
- Even after an explanation in a carefully monitored system only 45% could explain randomization
    - Weinfurt et al; (Med Care 2017;55: 970–978)
- Magnified when the research subject (participant) is viewed as vulnerable
- Some similar issues as with children
- Special issues with dependent adults
  - Assessing authenticity and capacity - Nat Rev Neurol. 2011 May 24; 7(7): 410–414.

Research and Practice

- Clinicians in general, especially in the US, are under tremendous pressure to generate revenue for practice and generally overwhelmed
- The majority of Americans say they would participate in clinical trials if asked by their clinicians, but the majority are never asked
- Asking someone to participate in a trial engenders a discussion about uncertainty and risk that often doesn't occur when delivering unproven treatments in practice
- Clinicians who work with older adults are even more stressed by overwhelming workload and financial pressure
- The discussion is likely to well beyond the individual

Advances in Clinical Trials Methods

- Person centered design
- Quality by design (adaptive design methods)
  - Simplify when possible
  - Add complex information with modern computing
  - Design adaptive to purpose of the trial
- Adaptive analytical methods
  - More ability to “learn as you go”
- Virtual and digital transformation
- Alternative randomization or quasi-experimental approaches
  - Cluster randomization
  - Stepped wedge
  - N of 1 trials
- “Synthetic control groups”
- Randomization within the real world
  - Using real world data + randomization to produce real world data

Clinical Trials in Older Adults-3 Key Time Frames

- Early in development
  - pK/pD studies specific to the intended use of the product
  - Drug interactions and human factors
- Pivotal clinical trials
  - Match the trial population to the likely patients who will receive prescriptions
  - Consider special complementary trials for drugs likely to have major use in older adults
  - Consider nested subgroups design
- Late phase/post market
  - Randomization in the real world
  - Interdigitation with observational real world evidence

Key Issue for pK/pD and Registration Trials

- What is the appropriate approach to requirements vs guidance in hopes it will be followed?
- Quote from anonymous Pharma leader (paraphrased):
  - “When we bring up trials in older age, the business people ask about the business case. What’s the return on investment? Since the drugs will be prescribed anyway, we don’t have a good argument based on net present value. But if FDA told us it’s required, we’d do it!”

Digital Transformation

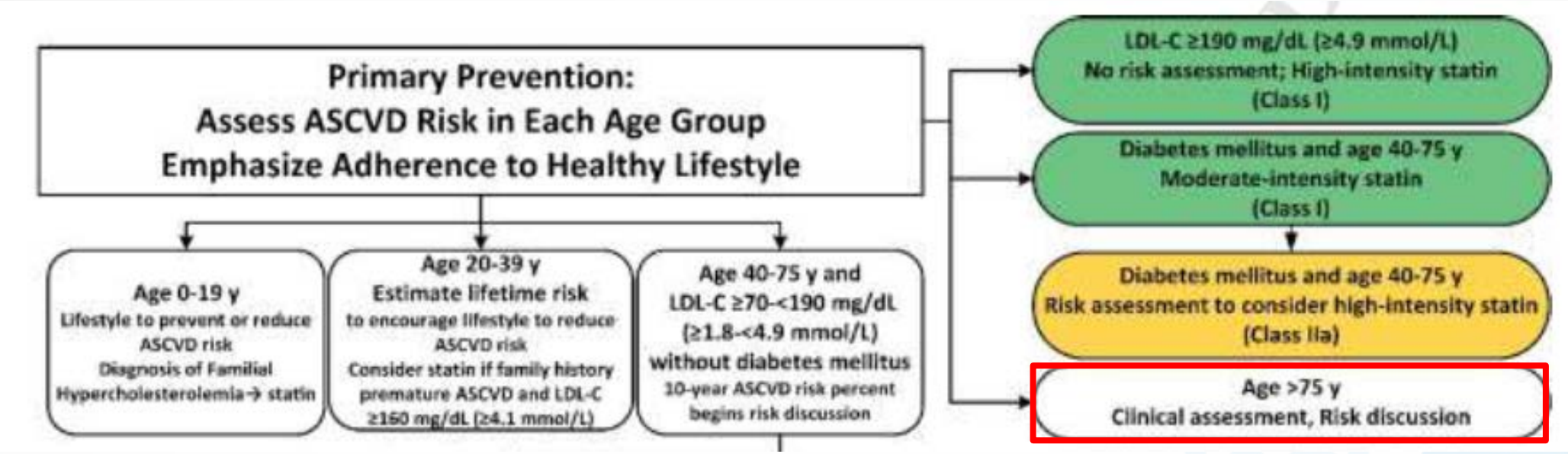
- Double edged sword
- Digital changes enable transformation (”home inversion”)
- Keeping people at home rather than institutionalized
- Virtual studies to enable insight into home environment
- Upscaling both research and clinical care with broader workforce able to provide care/do studies in the home
- New ability to deal with multiple dimensions due to massive change in computing
  - Biology
  - Behavior-Environment

Statins Are Effective for…

- Secondary prevention of CV events in those w/CVD
- Primary prevention of CV events up to age 75
- Primary prevention over age 75, particularly in the setting of multiple chronic conditions
- Other common conditions such as MCI/dementia, functional decline, or HFpEF

Best avenue is likely to be effective prevention.

2018 AHA ACC Cholesterol Guidelines



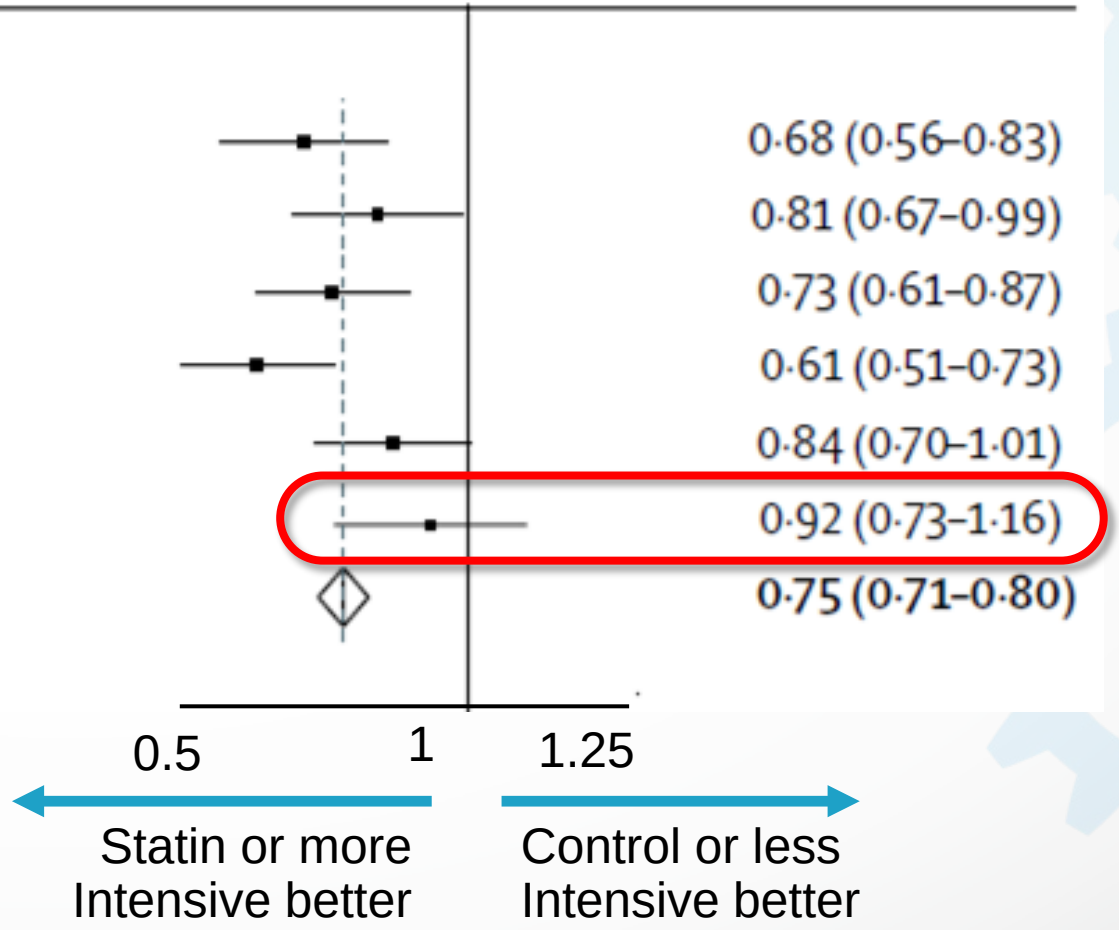
COR	LOE	Recommendations
IIb	B-R	1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (S4.4.4.1-1–S4.4.4.1-8)
IIb	B-R	2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy (S4.4.4.1-9).

Grundy JACC 2018

Meta-analysis of Cholesterol Treatment Trialists

Age >75 (N=6,449)
HR 0.92 (0.73 – 1.16)

	Events per Annum: Statin or more intensive	Events per Annum: Control or less intensive	
Participants without vascular disease			
≤55 years	290 (0·8)	408 (1·2)	0·68 (0·56–0·83)
>55 to ≤60 years	350 (1·0)	415 (1·2)	0·81 (0·67–0·99)
>60 to ≤65 years	416 (1·1)	545 (1·5)	0·73 (0·61–0·87)
>65 to ≤70 years	374 (1·2)	581 (1·8)	0·61 (0·51–0·73)
>70 to ≤75 years	400 (2·1)	462 (2·4)	0·84 (0·70–1·01)
>75 years	295 (2·7)	308 (2·8)	0·92 (0·73–1·16)
Total	**2125 (1·3)**	**2719 (1·6)**	**0·75 (0·71–0·80)**
Trend test χ^2_1=3·85 (p=0·05)			



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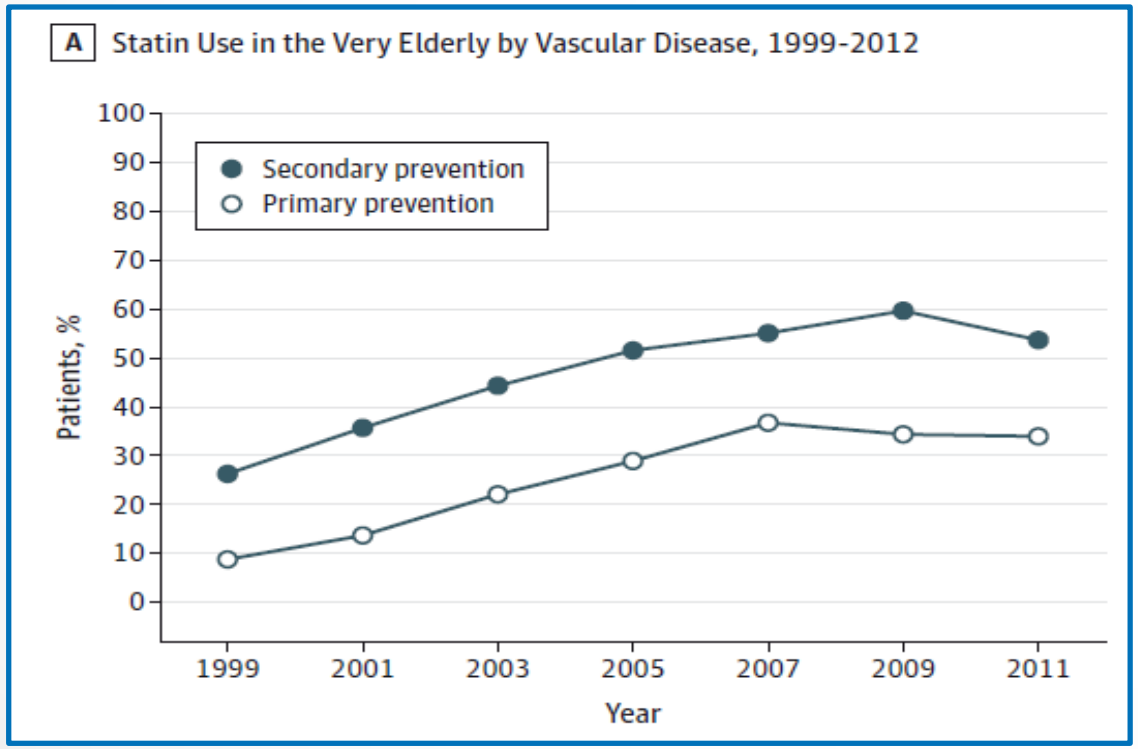
Lancet 2019; 393: 407–15

Prevalent Use and Equipoise

Older adults (>79 years)- Medical Expenditure Panel (AHRQ, CDC)



REF: Johannsen JAMA IM 2015;175: 1715-16

Older Adults (≥75 years) without CVD (PCORnet)

- N=1,722,860
  - 16% DM (N=282,932)
  - 63% female (N=1,078,333)
- Statin Users
  - 31% on a Statin (mostly prevalent use)
  - 51% of DM on a Statin

Trial Hypotheses

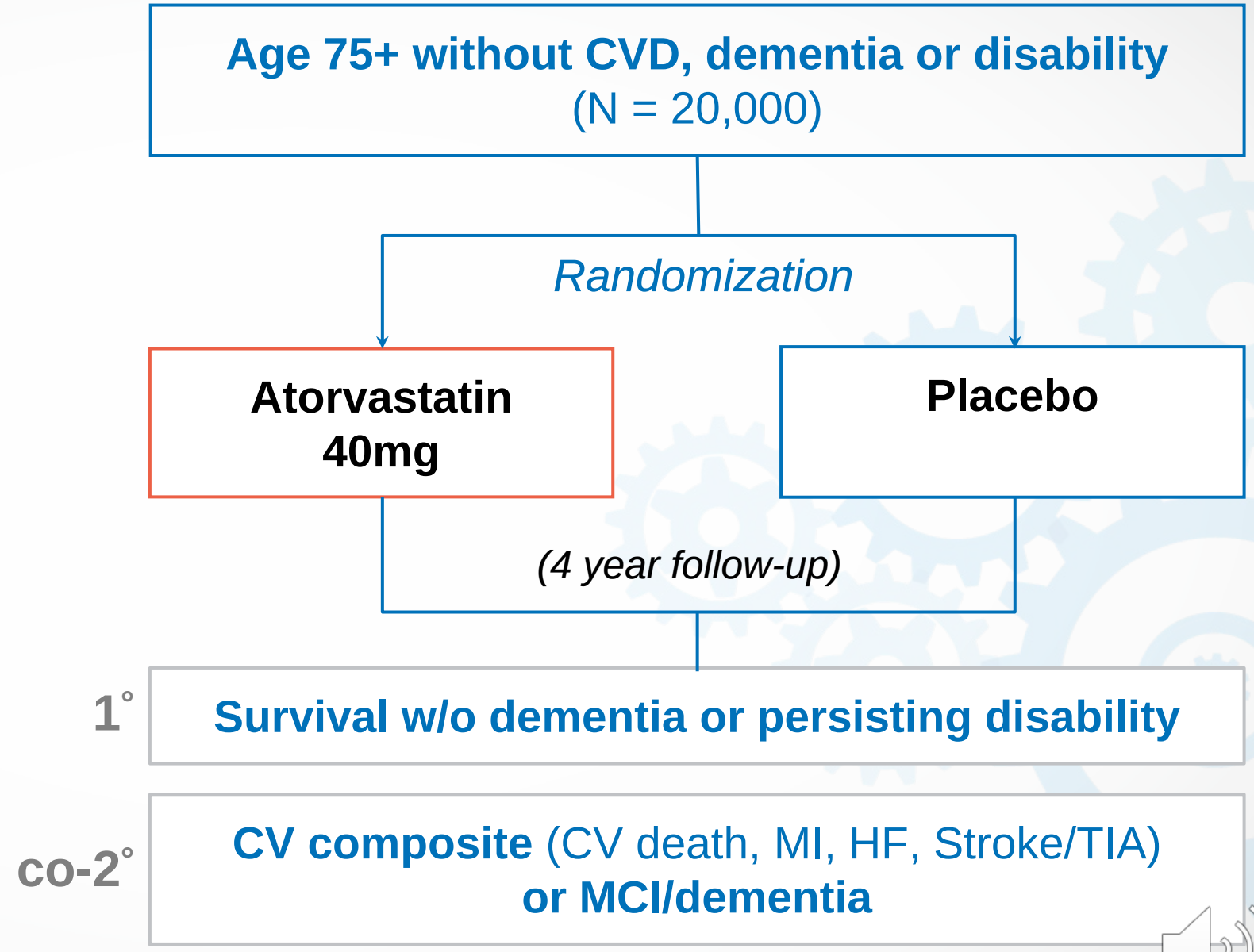
Primary Statins will reduce the occurrence of the composite of death, dementia, and persistent disability in community-dwelling older adults without cardiovascular disease (CVD) or dementia at baseline

Secondary Statins will reduce the occurrence of the co-secondary composites of MCI or dementia and CV composite outcome

Trial Design

Participants will:

- Be randomly assigned to atorvastatin 40 mg daily or matching placebo.
- Be followed through yearly phone calls for close to four years.
- Receive cognitive and physical function testing at screening, over the phone, and at home, if triggered.



Eligibility

- Community dwelling adults age ≥ 75 years
- No evidence or history of MI, stroke, revascularization, *or obstructive cardiovascular or peripheral vascular disease for which a statin is prescribed*
- No HF hospitalization in the last 12 months[1]
- No significant disability that limits independence[2]
- No dementia (clinical diagnosis or identified by staff)
- No contraindication to statins (active liver dz, intolerance)
- No statin use in the last 12 months[3]
- Severe hearing or visual impairment *(preventing follow-up)*

[1]Prior HF is not an exclusion
[2]Dependence in any Katz ADL (*except urinary or bowel continence*)
[3]Or longer than 5 years continually at any time

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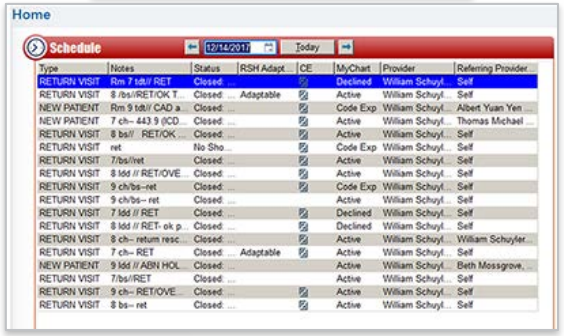
Enrollment to Randomization

Cohort Query Direct Approach

Patient/Clinician Engagement



Consent Baseline Data Collection

Baseline Cognitive Tests

Study Drug Assignment

X — X — X — X — X

Potential Population

Chart Review Confirm Eligibility

Clinic (Telehealth)

ENROLL

PREVENTABLE Call Center

RANDOMIZE

PREVENTABLE

Primary Endpoint Ascertainment

Survival Free of New Dementia or Persistent Disability

Survival

All-cause death

Beneficiary Status Change
+
National Death Index
+
Site Death Page

Dementia

Cognitive battery/adjudicated by experts

Persistent Disability

Loss of one Katz Basic ADL for > 90 days

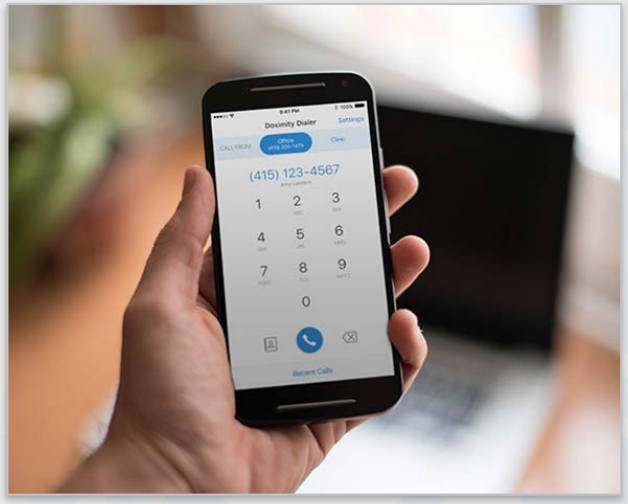
Call Center
+
Hawthorne Effect
(Year 1)

Telehealth-enabled Enrollment

Need to Avoid In-Person Visits?

OPTIONS:

Video
(Zoom/Webex)



Phone
(Doximity)

Challenges:

Technology

Biospecimen collection not required

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E-Consent

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PREVENTABLE

Preventable Consent_ Part 1

Consent to Participate in a Research Study

You are invited to take part in a clinical research study called PREVENTABLE. This research will take place at several different study site locations. This consent form includes two parts. Part 1 is the Main Consent and includes information that applies to all study sites. Part 2 is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together make up the complete consent form. You will be given a copy of the consent form.

Please take your time in reviewing this form. Ask your study doctor or the study staff to explain any words or information you don't know. You may also discuss the study with your primary care doctor, your family, and friends.

Page 1 of 11

Before we begin the consent, do you want us to show you how to make the words bigger on the page so they are easier to read?

Yes

No

reset

Institutional Review Board
Informed Consent Document for Research

Study Title: PREVENTABLE (PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in older adults)
Revision Date: X/XX/2020

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PREVENTABLE

Part_2_Wake Forest Baptist Hospital

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PAYMENT AND COSTS AND USE OF HEALTH INFORMATION FOR RESEARCH

Will I be paid for being in this study?
You will be paid $XX for your time and general expenses such as parking.

Are there costs to me for being in this study?
All tests and the study drug that are needed for this study that are not part of your usual medical care will be paid by the study.

Usual medical care is care you would receive whether or not you are part of this study. Your health insurance provider will be billed for your usual medical care.

What is Protected Health Information (PHI)?
The PHI collected for this research study includes your name, address, phone number, email address, date of birth, Social Security number, Medicare Beneficiary Identifier, and health information.

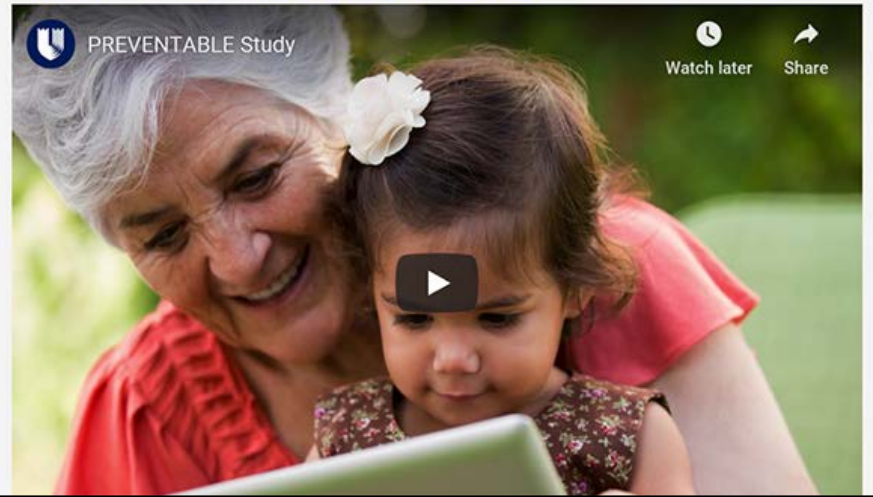
Will my PHI remain private?
We will make every effort to keep your PHI safe. We will store records in a locked cabinet or office or on a password-protected computer. Your identity and your PHI will not be shared unless it is required to protect your safety, the safety of others, or if you give us approval to share it.

Who will have access to or receive my PHI?
Your PHI may be given to others only if needed for reasons like carrying out the study, determining the results of the study, making sure the study is being done correctly, and providing required reports.

Some of those that may disclose your PHI are:

You are being invited to participate in the PREVENTABLE (PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults), a study in about 20,000 participants from many sites across the United States. Part 1 has information about the main study and Part 2 has information about your study site. Your participation is voluntary. Please consider the following information in making your decision.

Please watch the video below to learn more about the PREVENTABLE study.



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STATEMENT OF CONSENT

My signature below indicates that I have read and understood this consent form. I have had enough time and opportunity to think about the information, ask questions, and get my questions answered to my satisfaction. I understand that I am under no obligation to participate in this study, but I am willing to participate, and I am freely giving my consent to participate in the PREVENTABLE study. A copy of this form will be given to you.

Participant:

Name

Please sign using "add signature". ----------> Add signature

Date 2020-05-18

Study doctor or designee who obtained consent:

Name

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After Enrollment – Low touch Central and Site Partnership (no study visits)

	CENTRAL	SITE
Drug renewal	Shipping direct to participant	Annual renewal confirmation
Retention	Newsletters, community connections	Clinical support and equipoise
Lost to follow-up	Unable-to-contact list	Track down via EHR or local contact

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Some Possible Actions

- Use of legal requirements (sticks) to ensure that basic questions are answered prior to marketing
- Use of incentives to help industry take on the added risk and cost (carrots)
- Create Office or working group at FDA that can work with NIA and CMS on these issues
- Create funding and structure for multiple comorbidity research and development
- Integrate research and clinical care
- Deal with tension on protecting vulnerable people vs participation in research
- Take advantage of digital transformation
- Special focus on people housed in post-acute care facilities (long-term care, nursing homes, hospice)

Should we go the route of BPCA/PREA?
Older Adults: Similarities and Differences from Children

- Both groups have been ”therapeutic orphans”
- Both groups are not homogeneous
- Everyone knows that in the absence of good studies prescriptions will still be written for the same intended uses that are supported by evidence in younger adults
- Behaviorally and socially, there are issues that do not pertain to the general adult population
  - Nurseries, schools in children
  - Long-term care facilities in older adults
- Many of the issues relate to drugs that have already become generic and therefore have no manufacturer with major research capabilities
- Studies in either population are likely to raise uncomfortable questions that may be expensive or increase risk to the ”asset”
- Inclusion of either population increases the risk to the manufacturer that the label will be “dirty” because of higher levels of adverse events or otherwise unexpected outcomes
- In the absence of requirements/rewards (“sticks and carrots”) manufacturers are unlikely to directly address the needs of these special populations

NIH Clinical Center

- Should be ideal place to do pK/pD studies for drugs already off patent or nearing that point

Bottom Line

- Require pK/pD and human factors studies if intended use includes older adults
- Require specific consideration of including representative sample of older adults in registration trials
- Require specific RWE in the post-market driven by specific likely uses of the medication
- Form an FDA Office on older adults and charge it to collaborate across HHS
- Work with multiple sectors to advance the framework so the whole becomes much greater than the sum of the parts