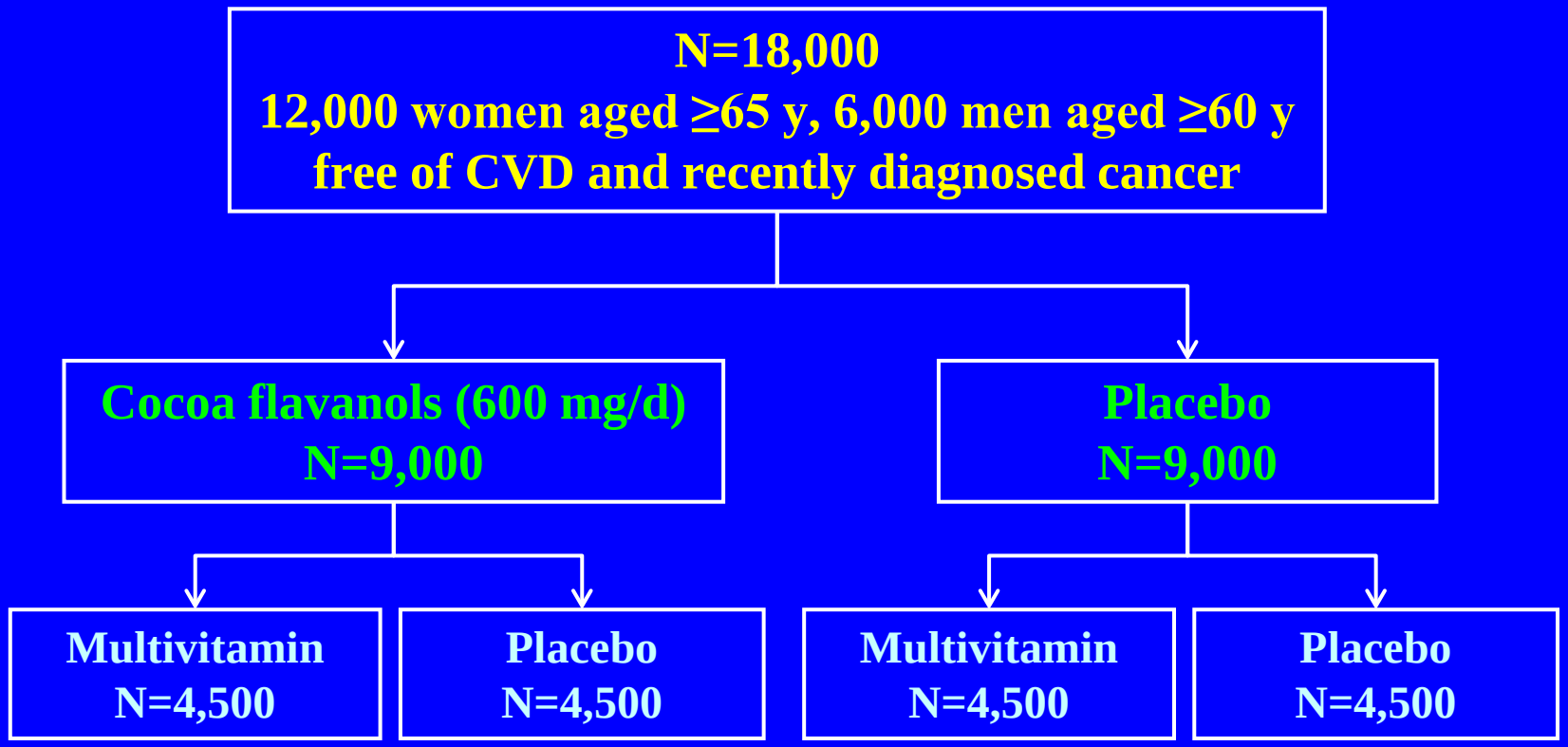
The *CO*coa *S*upplement and *M*ultivitamin *O*utcomes *S*tudy (COSMOS): A Randomized Trial of Cocoa Flavanols and Multivitamins in the Prevention of CVD and Cancer

JoAnn E. Manson, MD, DrPH
Howard D. Sesso, ScD, MPH
Brigham and Women's Hospital
Harvard Medical School

Garnet L. Anderson, PhD
Fred Hutchinson Cancer Research Center

WHI Investigators Meeting
May 4, 2017

COcoa Supplement and Multivitamin Outcomes Study (COSMOS)



Mean Treatment Period = 4.0 years.

Primary Outcomes: Major cardiovascular events (MI, stroke, CVD death, and coronary revascularization) and total cancer (excluding non-melanoma skin cancer).

Baseline Blood/Urine Collection: ~6000 participants; F/U samples in a subgroup.

Baseline Clinic Visit: Subcohort of ~500 Boston-based participants.

COSMOS Recruitment: Run-in and Randomization

- As of April 2017, 28,506 willing and eligible participants have started the placebo run-in
  - 8,673 women from WHI (N = 71,518 invited)
  - 9,260 women and 10,548 men enrolled through Brigham and Women's Hospital (BWH, including respondents from VITAL, mass mailings, and volunteers)
- 10,415 participants have been randomized
  - 4,523 WHI women (invited first; nearly complete)
  - 2,322 BWH women and 3,570 BWH men (mailings still in process)
  - 9,313 participants are currently in the run-in
- Invitational and run-in mailings will continue until we reach our target of 18,000 randomized.

COSMOS Biospecimen Collection

- **Supported through Mars Symbioscience and NIH grants.**
- ***Timeline and anticipated sample size of blood collections***
  - **Baseline: n=6,000**
  - **Year 1 repeat: n=1,000**
  - **Year 2 repeat: n=1,000**
  - **Year 4 repeat: n=1,000**
- ***Home visit via Examination Management Services Inc (EMSI)***
  - **Fasting blood and urine collection**
  - **Seated BP**
  - **Height, weight, waist and hip circumference**
- **Participants can also collect blood and urine on their own or by visiting a Quest Diagnostics center around the U.S.**
- **Ideal opportunity for studies of biomarkers and genetic factors.**

COSMOS Clinic Visits

- ***Timeline and sample size of clinic visits at BWH, Boston:***
  - **Baseline and 2-year follow-up**
  - **~600 women and men**
- ***In-depth assessments at clinical visits:***
  - **Fasting blood, spot urine, fecal sample collection**
  - **Seated and 24-hour ambulatory BP**
  - **Anthropometry**
  - **Cognitive function**
  - **Physical function**
  - **Pulse-wave velocity (PWV) and pulse-wave analysis (PWA)**
  - **Brain MRI**

Cognitive Ancillary Studies Update

- **Invitational mailings started in July 2016.**
- **As of April 2017, a total of 8,786 participants have been invited to participate in COSMOS Mind and/or COSMOS Web.**

Invited to COSMOS Mind and Web	Willing to participate in COSMOS Mind	Forwarded to COSMOS Mind	Willing to participate in COSMOS Web	COSMOS Web Email Link Sent
8,786	4,750	4,300	4,455	3,397

Other Pending Ancillary Studies

- **COSMOS Eye (NIH/NEI funded): will assess cataract and age-related macular degeneration.**
- **COSMOS Diabetes (resubmitted and to be reviewed June 2017)**
- **COSMOS Cancer (under development)**
- **COSMOS Heart Failure (under development)**

Conclusions: Overview

- Cocoa flavanols and multivitamins remain promising interventions for reducing risks of CVD and cancer, but conclusive evidence for their efficacy is lacking.
- The COSMOS trial will be the first large-scale RCT of cocoa extract in either men or women and the first large-scale trial of multivitamins in women.
- Recruitment for the trial is ongoing and proceeding well.

Lessons Learned

- **Pilot study projection for WHI participants = 12,000.**
- **Actual WHI participants randomized = 4,500 (37.5%).**
- **Of N=71,518 WHI participants invited, 6.3% were randomized.**
- **Preliminary: Stopped taking study pills after randomization**

  WHI participants: 5.1% (228 of 4,491)

  Non-WHI participants: 1.8% (100 of 5,444)

  (Need to assess role of age vs other factors)

Message: WHI participants are very dedicated to WHI and try to participate, but constraints are real.

Logistical/Operational Issues/Costs

- **Harmonization of data collection forms, outcomes assessment, endpoint adjudication (most relevant if study has both WHI and non-WHI participants).**
- **IRB coordination.**
- **Data transfer issues between BWH and FHCRC.**
- **Need clear demarcation of responsibilities at sites.**
- **Possible confusion by study participants whether to call BWH, FHCRC, or RCs.**
- **Added costs.**

Recommendations

- **Avoid RCTs that require recruitment of both WHI and non-WHI participants.**
- **Trials targeting participants with specific medical conditions or addressing topics of special interest to an aging population may have higher recruitment rates.**
- **Avoid long-duration RCTs (may discourage participation).**
- **Avoid study pills/capsules that pose any challenges for older participants to swallow.**
- **Minimize time commitment required of participants.**

Thank you!