The COcoa Supplement and Multivitamin Outcomes Study (COSMOS): A Randomized Trial of Cocoa Flavanols and Multivitamins in the Prevention of CVD and Cancer

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WHI Investigators Meeting
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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
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.

<table>
<thead>
<tr>
<th>Invited to COSMOS Mind and Web</th>
<th>Willing to participate in COSMOS Mind</th>
<th>Forwarded to COSMOS Mind</th>
<th>Willing to participate in COSMOS Web</th>
<th>COSMOS Web Email Link Sent</th>
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<tbody>
<tr>
<td>8,786</td>
<td>4,750</td>
<td>4,300</td>
<td>4,455</td>
<td>3,397</td>
</tr>
</tbody>
</table>
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!