Introduction to WHI
From inception to current Extension study:
Overview of WHI Protocol and study components and results

Garnet Anderson
WHI Clinical Coordinating Center
Fred Hutchinson Cancer Research Center
September 9, 2015
Women’s Health Initiative: Original objectives

Dr. Bernadine Healy, Former Director of NIH

• To test three chronic disease prevention strategies in full scale randomized trials:
  • Hormone therapy (HT)
  • A low-fat diet (Dietary Modification, DM)
  • Calcium & vitamin D supplements (CaD)

• To identify risk factors for the major causes of morbidity and mortality in post-menopausal women

Hormone Therapy Trials
• Primary: Coronary Heart Disease
• Secondary: Hip Fracture
• Safety: Breast Cancer

Calcium/Vitamin D Trial:
• Primary: Hip fractures
• Secondary: Colorectal Cancer

Dietary Modification Trial:
• Primary: Breast Cancer and Colorectal Cancer
• Secondary: Coronary Heart Disease

Observational Study

Total: 161,808 women

Thanks to the WHI participants
WHI participants

• Inclusion criteria
  • Postmenopausal, 50-79 years of age
  • Expected survival > 3 years
  • Likely to live in the area for 3 years
  • Willing to provide written informed consent

• Exclusion criteria specific to each trial based on
  • Safety
  • Adherence
  • Competing risk
Participants recruited by 40 Clinical Centers, 1993-1998
WHI recruitment

• Emphasis on assuring representation of minorities consistent with population in this age-group

• Age-specific goals and actual distribution for each CT component (as % of total):

<table>
<thead>
<tr>
<th>Age Interval</th>
<th>Goal</th>
<th>E-alone</th>
<th>E+P</th>
<th>DM</th>
<th>CaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>10</td>
<td>13</td>
<td>12</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>55-59</td>
<td>20</td>
<td>18</td>
<td>21</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>60-69</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>70-79</td>
<td>25</td>
<td>24</td>
<td>22</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

Follow-up and Outcomes collection

• CT—semi-annual contacts with annual clinic visits required
  • Intervention adherence
  • Brief physical exam
  • Mammography, breast exam, ECG (q3 years)
  • Medical history update (Form 33)
  • “6% subsample” randomly selected at baseline for additional data collection

• OS—annual mail follow-up (F33), limited exposure assessments and clinic visit at 3 years

• Documentation and adjudication of priority health events
  • CHD and related outcomes
  • Cancer
  • Hip Fracture
  • All deaths

Hormone therapy trial design

Hysterectomy

YES
N= 10,739

Conjugated equine estrogen (CEE 0.625 mg/d)
[aka ERT, E-alone, CEE]

Placebo

NO
N= 16,608

CEE + medroxyprogesterone acetate (CEE+MPA 2.5 mg/d)
[aka PERT, E+P, CEE+MPA]

Placebo

### Statistical power for the hormone therapy component

<table>
<thead>
<tr>
<th></th>
<th>Power % at Selected Sample Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women with Uterus (55%)</td>
</tr>
<tr>
<td></td>
<td>Women (45%)</td>
</tr>
<tr>
<td></td>
<td>Hysterectomized</td>
</tr>
<tr>
<td></td>
<td>PERT vs. Placebo</td>
</tr>
<tr>
<td></td>
<td>ERT vs. Placebo</td>
</tr>
<tr>
<td>Intervention</td>
<td>Average Disease Probability (× 100)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Hip Fractures</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Combined Fractures</td>
<td>20</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>22</td>
</tr>
</tbody>
</table>

* = Absolute value of one minus intervention versus control incidence rates at planned study termination, multiplied by 100.

— = Power for design assumption based on a weighted logrank statistic highlighted.
A New Study Raises Fears About the Risks For Millions Of Women. Here's What You Should Do

Beyond Hormone Therapy

JULY 22, 2002

WALL STREET: LOSING SAVINGS—AND TRUST

THE TRUTH ABOUT HORMONES

Susan Platero, 60, of Miami, has been on hormones for 10 years. She is angry and confused but not yet ready to stop taking them.

Hormone-replacement therapy is riskier than advertised. What's a woman to do?
E+P monitoring boundaries and results, continued

Invasive Breast Cancer
Stopping Boundaries and Observed Z-values

Global Index
Stopping Boundaries and Observed Z-values

Clinical Outcomes in the WHI Postmenopausal Hormone Therapy Trials—Intervention phase results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estrogen+Progestin</th>
<th>Estrogen-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.29</td>
<td>1.02 - 1.63</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>1.07 - 1.85</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.11</td>
<td>1.58 - 2.82</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26</td>
<td>1.00 - 1.59</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>0.43 - 0.92</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.83</td>
<td>0.47 - 1.47</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66</td>
<td>0.45 - 0.98</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>0.92</td>
<td>0.74 - 1.14</td>
</tr>
<tr>
<td>Global index</td>
<td>1.15</td>
<td>1.03 - 1.28</td>
</tr>
</tbody>
</table>

WHI Study Group, JAMA 2002; WHI Steering Committee, JAMA 2004
Clinical Outcomes in the WHI Postmenopausal Hormone Therapy Trials—Intervention phase results

<table>
<thead>
<tr>
<th>Event</th>
<th>Estrogen+Progestin</th>
<th>Estrogen-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.29</td>
<td>1.02 - 1.63</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>1.07 - 1.85</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.11</td>
<td>1.58 - 2.82</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26</td>
<td>1.00 - 1.59</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>0.43 - 0.92</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.83</td>
<td>0.47 - 1.47</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66</td>
<td>0.45 - 0.98</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>0.92</td>
<td>0.74 - 1.14</td>
</tr>
<tr>
<td>Global index</td>
<td>1.15</td>
<td>1.03 - 1.28</td>
</tr>
</tbody>
</table>

WHI Study Group, JAMA 2002; WHI Steering Committee, JAMA 2004
Clinical Outcomes in the WHI Postmenopausal Hormone Therapy Trials—Intervention phase results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estrogen+progestin</th>
<th>95% CI</th>
<th>Estrogen-alone</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>1.29</td>
<td>1.02 - 1.63</td>
<td>0.91</td>
<td>0.75 - 1.12</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>1.07 - 1.85</td>
<td>1.39</td>
<td>1.10 - 1.77</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.11</td>
<td>1.58 - 2.82</td>
<td>1.33</td>
<td>0.99 - 1.79</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26</td>
<td>1.00 - 1.59</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>0.43 - 0.92</td>
<td>1.08</td>
<td>0.75 - 1.55</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.83</td>
<td>0.47 - 1.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66</td>
<td>0.45 - 0.98</td>
<td>0.61</td>
<td>0.41 - 0.91</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>0.92</td>
<td>0.74 - 1.14</td>
<td>1.08</td>
<td>0.88 - 1.32</td>
</tr>
<tr>
<td>Global index</td>
<td>1.15</td>
<td>1.03 - 1.28</td>
<td>1.01</td>
<td>0.91 - 1.12</td>
</tr>
</tbody>
</table>

WHI Study Group, JAMA 2002; WHI Steering Committee, JAMA 2004
Hypotheses in the DM trial

1° Does a low fat dietary pattern reduce breast cancer incidence?
1° Does a low fat diet reduce colorectal cancer incidence?
2° Does a low fat diet reduce CHD incidence?

Note: 2:3 randomization used to reduce costs

19,541 Intervention: Low-fat eating pattern
  • Aim for 20% calories from fat
  • Increase fruits/vegetables/grains

48,835 randomized

29,294 Comparison: Usual diet

84% power to observe a 14% reduction in breast cancer rates after 8.5 years (mean) follow-up [Anderson et al., Ann Epidemiol 2003]
Intervention group achieved ~70% of the change in dietary intake specified in the design.
DM trial found a modest but non-significant benefit for breast cancer but not for colorectal cancer (or CHD)

Invasive breast cancer incidence
Prentice RL et al. JAMA 2006

Colorectal cancer incidence
Beresford SAA et al, JAMA 2006
Women with higher baseline fat intake made bigger changes in fat intake and experienced somewhat greater risk reduction: A case-case analysis using 4DFRs

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% energy from fat (kcal)</td>
<td>(Number of cases = 655)</td>
<td>(Number of cases = 1072)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 27.9</td>
<td>144</td>
<td>222</td>
<td>0.97 (0.79, 1.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>27.9 - &lt; 32.3</td>
<td>186</td>
<td>259</td>
<td>1.08 (0.89, 1.30)</td>
<td></td>
</tr>
<tr>
<td>32.3 - &lt; 36.8</td>
<td>160</td>
<td>283</td>
<td>0.85 (0.70, 1.03)</td>
<td></td>
</tr>
<tr>
<td>≥ 36.8</td>
<td>151</td>
<td>291</td>
<td>0.78 (0.64, 0.95)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vegetables and fruits (sv/day)</th>
<th>(Number of cases = 655)</th>
<th>(Number of cases = 1072)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.3</td>
<td>155</td>
<td>259</td>
<td>0.90 (0.73, 1.09)</td>
<td>0.07</td>
</tr>
<tr>
<td>2.3 - &lt; 3.3</td>
<td>158</td>
<td>268</td>
<td>0.88 (0.72, 1.07)</td>
<td></td>
</tr>
<tr>
<td>3.3 - &lt; 4.6</td>
<td>144</td>
<td>264</td>
<td>0.82 (0.67, 1.00)</td>
<td></td>
</tr>
<tr>
<td>≥ 4.6</td>
<td>197</td>
<td>276</td>
<td>1.08 (0.90, 1.29)</td>
<td></td>
</tr>
</tbody>
</table>

Prentice RL et al. JAMA 2006
Trial results motivate search for nutrition biomarkers to better calibrate self-reported intake and improve inference

Prentice et al, AJE 2013

<table>
<thead>
<tr>
<th>Energy Calibration by Group</th>
<th>Control for BMI$^{a,c}$</th>
<th>Fat Density</th>
<th>Total Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Combined cohorts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.05</td>
<td>1.01, 1.09</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.03</td>
<td>0.99, 1.07</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.04</td>
<td>1.00, 1.08</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1.05</td>
<td>1.00, 1.09</td>
</tr>
<tr>
<td>Dietary Modification Trial comparison group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.07</td>
<td>0.96, 1.18</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.03</td>
<td>0.92, 1.14</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.05</td>
<td>0.95, 1.16</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1.05</td>
<td>0.94, 1.17</td>
</tr>
<tr>
<td>Observational study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>1.05</td>
<td>1.01, 1.09</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.03</td>
<td>0.99, 1.08</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.04</td>
<td>1.00, 1.08</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1.05</td>
<td>1.00, 1.10</td>
</tr>
</tbody>
</table>

Table 4. Hazard Ratios$^{a}$ for a 40% Increment in Fat Density and a 20% Increment in Total Energy Consumption Based on FFQ Data From 5,061 Invasive Breast Cancer Cases and 98,365 Noncases From the Women’s Health Initiative Dietary Modification Trial Comparison Group and Observational Study Cohorts, 1994–2010

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio.

$^{a}$ Based on Cox regression on log(FFQ fat density), log(FFQ total energy), with and without biomarker calibration, date of cohort enrollment, race/ethnicity, education, smoking, postmenopausal hormone use (ever use of estrogen alone, ever use of estrogen plus progestin), Gall model risk score, and estimated recreational physical activity with
Calcium and Vitamin D (CaD) trial hypotheses and design

• 1° Does supplemental calcium and vitamin D reduce hip fracture rates?
• 2° Does calcium and vitamin D reduce colorectal cancer incidence?

Note: Randomization to CaD trial offered to HT and DM trial participants at/after year 1 visit

Calcium carbonate 1000 mg/d
+ vitamin D 400 IU/d

36,282 randomized (1:1)

Placebo

88% power to observe a 21% reduction in hip fracture rates after 7.5 years (mean) follow-up
[Anderson et al., Ann Epidemiol 2003]
CaD helps to preserve bone mineral density

- Greater preservation in total hip BMD
- Average differences between CaD and placebo groups:
  - 0.59% at AV3
  - 0.86% at AV6
  - 1.01% at AV9

Jackson et al., NEJM 354;7:669-683
Calcium and vitamin D supplements may slightly reduce risk of hip fracture; no benefit seen for colorectal cancer.

Hip fracture incidence

![Graph showing hip fracture incidence with hazard rate (HR) 0.88; 95% CI 0.72-1.08, P-value = 0.23.]

Colorectal cancer incidence

- **Hip fractures**
  - HR 0.88; 95% CI 0.72-1.08
  - 14 CaD vs 16 placebo

- **Lower arm or wrist fractures**
  - HR 1.01; 95% CI 0.90-1.14
  - 44 CaD vs 44 placebo

- **Total fractures**
  - HR 0.94; 95% CI 0.87-1.02
  - 164 CaD vs 170 placebo

Jackson et al., NEJM 354:7:669-683

Wactawski-Wende, et al., NEJM 2006;354:694-696
## Study timeline & significant events

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-98</td>
<td>Recruitment by 40 Clinical Centers</td>
</tr>
<tr>
<td>1994</td>
<td>Redesign of HT trial</td>
</tr>
<tr>
<td>2000</td>
<td>HT participants notified of adverse CVD effects</td>
</tr>
<tr>
<td>2001</td>
<td>HT participants informed that adverse CVD effects were continuing</td>
</tr>
<tr>
<td>2002</td>
<td>E+P trial intervention stopped by DSMB, all WHI participants notified, follow-up continued</td>
</tr>
<tr>
<td>2004</td>
<td>E-alone trial stopped by NHLBI, follow-up continued</td>
</tr>
<tr>
<td>2004-5</td>
<td>DM and CaD trials completed; Participants consented to longer-term, centralized follow-up; 39 Field Centers + CCC continue outcomes procedures (Extension I)</td>
</tr>
<tr>
<td>2010</td>
<td>Participants re-consented to extended, follow-up (Extension II); Outcomes documentation streamlined; 4 Regional Centers, 6 satellite sites and CCC</td>
</tr>
<tr>
<td>2012-13</td>
<td>Long-Life substudy implemented</td>
</tr>
<tr>
<td>2015</td>
<td>Centralized follow-up continues in Extension III</td>
</tr>
<tr>
<td>2015</td>
<td>WHISH and COSMOS trials begin</td>
</tr>
</tbody>
</table>
Protocol changes in the Extension Studies

• 2005-2010
  • CT follow-up reduced to annual, centralized, mailed follow-up (F33 and selected exposure updates)
  • Modest streamlining of outcomes data

• 2010-2015
  • Outcomes documentation/adjudication limited to HT/AA/Hispanic participants (Medical Records Cohort, MRC)
  • Self-Report Cohort (all others) receive annual follow-up
  • Long Life Study of ~8,000 older MRC participants have a home visit with brief physical exam, functional status assessment and blood collection

• 2015-2020
  • No significant changes
Study milestones may be important in analyses
Example: Breast cancer hazard ratios during and after intervention in the E+P trial

P = 0.28 for difference in trend
P = 0.005 for adherence-adjusted difference in trend

Cohort attrition by study phase

• 161,808 participants from 40 U.S. centers followed for up to 12 years (1993-2005)
• 115,403 participants enrolled in WHI Extension Study I (2005-2010)
• 93,500 participants enrolled in WHI Extension Study II (2010-2015)
• ~78,000 currently alive and in active follow-up
• Passive follow-up data
  • Linkage to Medicare established for ~142,000 women (96% of those with valid social security numbers)
  • NDI searches to determine vital status and cause of death
Age distribution of active participants on September 30, 2015 (N=81,330)

- <75: 3972 MRC, 11608 SRC
- 75-79: 5223 MRC, 16803 SRC
- 80-84: 4649 MRC, 15751 SRC
- 85-89: 3486 MRC, 12134 SRC
- 90-94: 1424 MRC, 5115 SRC
- 95+: 254 MRC, 911 SRC

Legend:
- MRC: Blue
- SRC: Orange
WHI cohort composition changes over time

- American Indian
- Asian/Pacific Islander
- Black
- Hispanic
- White
- Unknown

Baseline, 2005, 2010
WHI organizations & functions

• Funding and oversight by NHLBI (Shari Ludlam, Program Officer)

• Clinical Coordinating Center (PI: Garnet Anderson)
  • Centralized mail follow-up
  • Coordinate outcomes adjudication
  • Support study committees, SIGs
  • Maintain databases and biospecimen repository @ Fisher Bioservices
  • Provide analytic support

• Four Regional Centers (PIs: Rebecca Jackson, Sally Shumaker, Marcia Stefanick, Jean Wactawski-Wende) and 5 satellite sites
  • Follow-up of mail non-responders
  • Document outcomes
  • Provide analytic support
  • Engage investigators/support SIGs
WHI Committees & Governance

• Steering Committee (Rebecca Jackson, chair)
• Outcomes Advisory Committee (Karen Margolis, chair)
• Ancillary Study Committee (Robert Brunner, chair)
• Publications and Presentations Committee (Barbara Howard and Cynthia Thomson, co-chairs)
• Scientific Resources Working Group (Rebecca Jackson, chair)
• Scientific Interest Groups
  • Aging, Bone/Fracture/Body Composition, Cancer, CVD, Genetics/Proteomics/Biomarkers, Health Services, Minorities & Health Disparities, Nutrition/Energy Balance, Obesity/Diabetes, Physical & Built Environment, Psychosocial & Behavior Health
Study Policies: Publications and Presentations

• Manuscript proposals, including analytic plan must be approved by P&P and writing committee membership offered to WHI investigators
• Final manuscript must be approved by P&P prior to journal submission
• Meeting abstracts need prior approval by P&P
• All papers must acknowledge WHI funding, investigators

Additional information at
https://www.whi.org/researchers/SitePages/Write%20a%20Paper.aspx
Study Policies: Ancillary Studies

• Definition: Any study that generates new data not covered by the WHI protocol
  • New questionnaires
  • Analyses of biospecimens
  • Linkage to external data

• Approvals
  • All proposed ancillary studies must be reviewed and recommended by the ASC and approved by the Steering Committee and NHLBI
  • Ancillary studies with participant burden must be reviewed by the DSMB

Additional information at:
https://www.whi.org/researchers/SitePages/Ancillary%20Studies%20Overview.aspx
WHIMS suite of studies in HT participants

The Women’s Health Initiative Memory Study (WHIMS)
The Women’s Health Initiative Memory Study (WHIMS) Extension
The Women’s Health Initiative Memory Study - Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)
The Women’s Health Initiative Memory Study of Younger Women (WHIMS-Y)
The Women’s Health Initiative Study of Cognitive Aging (WHISCA)
The Women’s Health Initiative Study of Cognitive Aging (WHISCA) Extension
The Women’s Health Initiative Memory Study of Cerebral Magnetic Resonance Imaging (WHIMS-MRI-1+2)
Filling the gaps in WHI data and biospecimen collection for cancer survivorship and molecular epidemiology studies
A Pragmatic Trial: Physical Activity to Improve CV Health in Women

PIs: Marcia Stefanick, Charles Kooperberg, Andrea LaCroix, Ph.D

Eligible based on existing data

- no: Follow, per WHI protocol
- yes: Randomize
  - Control (n ~ 25,000)
  - Intervention (n ~ 25,000)

Consent

- yes: WHISH PA (Go4Life®) Intervention deliver mail-based [+ website, etc.] ± IVR** (phone) + live advisor, PRN
- no: Opt Out
- yes: Follow, per WHI protocol

** Interactive Voice Response System (Consent)
**COcoa Supplement and Multivitamin Outcomes Study**

**PIs:** JoAnn E. Manson, Howard Sesso

WHI women aged ≥65 y + VITAL non-randomized men aged ≥60 y

- **Cocoa flavanols**
  - N=9,000
    - Multivitamin N=4,500
    - Placebo N=4,500

- **Placebo**
  - N=9,000
    - Multivitamin N=4,500
    - Placebo N=4,500

**Primary Outcomes:** Major cardiovascular events (MI, stroke, CVD death, and coronary revascularization) and total cancer (excluding non-melanoma skin cancer)
The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services

Contracts: HHSN2682011000046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, HHSN271201100004C)