WHI Medication Data

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Survey of:

- Medications inventoried during study period
- Medications self-reported during extension period(s)
- Analytic strategies
Medications: Study

- Inventoried on Form 44

<table>
<thead>
<tr>
<th>Study</th>
<th>Visit</th>
<th>Baseline (sv1 &amp; sv3)*</th>
<th>AV1</th>
<th>AV3</th>
<th>AV6</th>
<th>AV9</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>OS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Typically 66(47, 102) days apart.*
Medications: Study (cont’d)

What is collected

• Prescription and OTC medications
  • Using medication at collection interview
  • OTC medications also required frequency of at least twice a week, for the last 2 weeks

• Medication info
  • Duration of current use
  • Name, generic name & National Drug Code
    • Therapeutic Class Code (TCCODE)
  • Strength
  • Ingredients
What is not collected

- Medication info
  - Frequency of use (e.g., BID)
  - Dosage (i.e., # of pills)
- Not vitamin/mineral supplements (F45)
## Medications: Study (cont’d)

### Data files

<table>
<thead>
<tr>
<th>Data File Name</th>
<th>Data Source</th>
<th>Data File Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>F44_ctos_inv</td>
<td>WHI Participants</td>
<td>WHI participant medication data (TCCODE) from baseline &amp; follow-up</td>
</tr>
<tr>
<td>F44ref_med_classes</td>
<td>Medi-Span</td>
<td>Therapeutic Class Details</td>
</tr>
<tr>
<td>F44ref_meds</td>
<td>Medi-Span</td>
<td>Medication Details</td>
</tr>
<tr>
<td>F44ref_med_ingreds</td>
<td>Medi-Span</td>
<td>Ingredient Details</td>
</tr>
</tbody>
</table>

F44ref_therclas.pdf (TCCODE dictionary)
Medications: Study (cont’d)

- Key resources
  - F44_ReadMe.pdf
    - Reference file descriptions
  - SAS code on how to extract data from F44_ctos_inv
    - Use usual variables for follow-up years: F44VTYP, F44VY, F44VCLO & F44EXPC
  - F44_ctos_inv
  - f44ref_therclas.pdf
Medications: Study (cont’d)

360000 ANTIHYPERTENSIVE
   361000 ACE INHIBITORS
   361500 ANGIOTENSIN II RECEPTOR ANTAGONIST
   362000 ANTIADRENERGIC ANTIHYPERTENSIVES
      362010 ANTIADRENERGICS - CENTRALLY ACTING
      362020 ANTIADRENERGICS - PERIPHERALLY ACTING
      362030 RESERPINE
   362500 SELECTIVE ALDOSTERONE RECEPTOR ANTAGONISTS (SARAS)
   363000 AGENTS FOR PHEOCHROMOCYTOMA
   364000 VASODILATORS
      364010 FLUOROQUINOLONE VASODILATORS
      364020 DOPAMINE D1 RECEPTOR AGONISTS
   365000 ANTIHYPERTENSIVE - MAOIS
   366000 MISC. ANTIHYPERTENSIVES
   369000 ANTIHYPERTENSIVE COMBINATIONS
      369910 RESERPINE COMBINATIONS
      369915 ACE INHIBITORS & CALCIUM BLOCKERS
      369918 ACE INHIBITORS & THIAZIDE/THIAZIDE-LIKE
      369920 BETA BLOCKER & DIURETIC COMBINATIONS
      369925 BETA BLOCKER & CALCIUM BLOCKER COMBINATIONS
      369940 ANGIOTENSIN II RECEPTOR ANTAGONISTS & THIAZIDES
Medications: Study (cont’d)

- F44ref_therclas.pdf (TCCODE dictionary)

360000 ANTIHYPERTENSIVE

361000 ACE INHIBITORS
361500 ANGIOTENSIN II RECEPTORS

362000 ANTIADRENERGIC DRUGS
362010 ANTIADRENERGIC DRUGS -中枢
362020 ANTIADRENERGIC DRUGS - peripheral
362030 RESERPINE

362500 SELECTIVE ALDOSTERONE RECEPTOR ANTAGONISTS

363000 AGENTS FOR PHOSPHATE REGULATION
364000 VASODILATORS
364010 FLUOROQUINOLONES
364020 DOPAMINE D1 RECEPTOR AGONISTS

365000 ANTIHYPERTENSIVES

366000 MISC. ANTIHYPERTENSIVES

369900 ANTIHYPERTENSIVE COMBINATIONS
369910 RESERPINE COMBINATIONS
369915 ACE INHIBITORS & CALCIUM CHANNEL BLOCKERS
369918 ACE INHIBITORS & THIAZIDE/DIURETICS

369920 BETA BLOCKER & DIURETIC COMBINATIONS
369925 BETA BLOCKER & CALCIUM BLOCKER COMBINATIONS
369940 ANGIOTENSIN II RECEPTOR ANTAGONISTS & THIAZIDES

370000 DIURETICS

371000 CARBONIC ANHYDRASE INHIBITORS
372000 LOOP DIURETICS
373000 MERCURIAL DIURETICS
374000 OSMOTIC DIURETICS
375000 POTASSIUM SPARING DIURETICS
376000 THIAZIDES AND THIAZIDE-LIKE DIURETICS
379000 MISCELLANEOUS DIURETICS
379900 COMBINATION DIURETICS
379910 DIURETICS & POTASSIUM
379920 NON PRESCRIPTION DIURETICS

330000 BETA BLOCKERS

331000 BETA BLOCKERS - NON-SELECTIVE
332000 BETA BLOCKERS - CARDIO-SELECTIVE
333000 ALPHA-BETA BLOCKERS

340000 CALCIUM BLOCKERS
Medications: Extension(s)

- Self-reported (mail) on Form 153

<table>
<thead>
<tr>
<th>Study</th>
<th>Visit</th>
<th>Ext I</th>
<th>Ext II</th>
<th>Non-responders were followed-up with a telephone call</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT&amp;OS</td>
<td></td>
<td>X</td>
<td></td>
<td>~ 97K</td>
</tr>
<tr>
<td>(MRC)</td>
<td></td>
<td></td>
<td>X</td>
<td>~ 18K</td>
</tr>
</tbody>
</table>

- WHI extension study I (2005-2010) collected at year five
- WHI extension study II (2010-2015) collected on MRC at year three
Medications: Extension (cont’d)

Data files

<table>
<thead>
<tr>
<th>Data File Name</th>
<th>F44 file</th>
<th>Data File Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>F153_medications_inv</td>
<td>F44_ctos_inv</td>
<td>WHI participant medication data (TCCODE) from baseline &amp; follow-up</td>
</tr>
<tr>
<td>F153ref_med_classes</td>
<td>F44ref_med_classes</td>
<td>Therapeutic Class Details</td>
</tr>
<tr>
<td>F153ref_meds</td>
<td>F44ref_meds</td>
<td>Medication Details</td>
</tr>
<tr>
<td>F153ref_med_ingredients</td>
<td>F44ref_med_ingredients</td>
<td>Ingredient Details</td>
</tr>
</tbody>
</table>

- F153ref_therclas.pdf (expanded TCCODEs)
- F153_ReadMe.pdf
Differences: F44 vs. F153

- F153 differentiates between prescription meds (section A) and OTC (section C)
- Limited to 10 prescription meds
- Somewhat expanded list of TCCODEs

Duration:

<table>
<thead>
<tr>
<th>UOM</th>
<th>D = Day</th>
<th>W = Week</th>
<th>M = Month</th>
<th>Y = Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VS

- Less than 1 month
- 1 to 12 months
- More than 1 year → How many years?
F153 Section C

- F44 collected any OTC meds
- Section collected only select OTC meds:
  - Aspirin, anti-inflammatory, antacid, natural female hormone, OTC insulin

<table>
<thead>
<tr>
<th>6.1 Are you taking over-the-counter insulin?</th>
<th>If you listed insulin as a prescription medication in Section A, do not include it again here.</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1 Yes →</td>
<td>Name of the product (listed on the bottle or package)</td>
</tr>
<tr>
<td>□ 0 No</td>
<td>How often do you take it?</td>
</tr>
<tr>
<td></td>
<td>□ 1 Once a day or more</td>
</tr>
<tr>
<td></td>
<td>□ 2 Less than once a day</td>
</tr>
<tr>
<td>Strength:</td>
<td></td>
</tr>
<tr>
<td>How long have you been taking it?</td>
<td></td>
</tr>
<tr>
<td>□ 1 Less than 1 month</td>
<td></td>
</tr>
<tr>
<td>□ 2 1 to 12 months</td>
<td></td>
</tr>
<tr>
<td>□ 3 More than 1 year</td>
<td></td>
</tr>
<tr>
<td>Number of years?</td>
<td></td>
</tr>
</tbody>
</table>
Beware of additional TCCODEs
- Use Ctrl+F
- F153
- F44

And look out for combinations
- Use Ctrl+F

- 390000 ANTIHYPERLIPIDEMICS
  - 391000 BILE ACID SEQUESTRANTS
  - 392000 FIBRIC ACID DERIVATIVES
  - 393000 INTESTINAL CHOLESTEROL ABSORPTION INHIBITORS
  - 394000 HMG COA REDUCTASE INHIBITORS
  - 394099 HMG COA REDUCTASE INHIBITOR COMBINATIONS
- 394500 NICOTINIC ACID DERIVATIVES
- 395000 ANTIHYPERLIPIDEMICS - MISC.
- 399900 ANTIHYPERLIPIDEMICS - COMBINATIONS
  - 399920 FIBRIC ACID DERITIVE COMBINATIONS
  - 399940 INTEST CHOLEST ABSORP INHIB-HMG COA REDUCTASE INHIB COMB

- 390000 ANTIHYPERLIPIDEMIC
  - 391000 BILE SEQUESTRANTS
  - 392000 FIBRIC ACID DERIVATIVES
  - 393000 INTESTINAL CHOLESTEROL ABSORPTION INHIBITORS
  - 394000 HMG COA REDUCTASE INHIBITORS
  - 394099 HMG COA REDUCTASE INHIBITOR COMBINATIONS
- 394500 NICOTINIC ACID DERIVATIVES
- 395000 MISC. ANTIHYPERLIPIDEMICS
- 399900 ANTIHYPERLIPIDEMIC COMBINATIONS
  - 399920 FIBRIC ACID DERITIVE COMBINATIONS

- 409900 MISC. CARDIOVASCULAR COMBINATIONS
- 409925 CALCIUM BLOCKER & HMG COA REDUCTASE INHIBITOR COMB
- 409925 CALCIUM BLOCKER & HMG COA REDUCTASE INHIBITOR COMB
Differential statin use between randomization arms

- ITT analysis is appropriate per expert panel recommendations to FDA (2010)
- No appreciable influence; did not confound WHI HT trial results (2016)
- Regardless, always good idea to perform sensitivity analysis

Statin use increased markedly with time for both arms
OS participants have less reliable history

\[ \text{OR}(95\%\text{CI}) = 0.76(0.71, 0.82); P < 0.001 \]
Analytic strategies (response)

- Consider a longitudinal analysis (GEE)
  - Select link function (e.g., logit)
  - Leverage within-person ‘correlation’
    - Log-odds ratio structure
  - Omnibus 1-df test

- Consider missing data assumptions
  - Missing Completely At Random vs Missing at Random
  - GEE assumes former
    - Consider limiting follow-up to Year
    - Weighted GEE
Analytic strategies (exposure)

- Differential reliability (CT vs. OS) and temporal trends
  - Censor medications that are out-of-date
    - Censoring window depends on context
    - Could use finer window for CT; covariate
  - Leverage self-reported duration
    - Refine initiation with duration
    - Careful with Extension I collection
      - Correct differential follow-up for non-users
Analytic strategies (exposure; cont’d)
Analytic strategies (exposure; cont’d)

- Baseline exposure is not adequate
- Time-dependent exposure should be used
- Unreliable medication use history manifests as measurement error in time-dependent exposure
- Risk estimates will be biased towards zero
Censor out-of-date medications to mitigate bias

Additional gains may be realized by refining estimated time of initiation by self-report of duration
Analytic strategies (cont’d)

- Exploratory Data Analysis (EDA) is extremely important
  - Critical in understanding
  - Association between exposure and outcome should **not** be part of EDA → Biased, overly optimistic results
**Analytic strategies (exposure; cont’d)**

### Example #1

<table>
<thead>
<tr>
<th>ID</th>
<th>study</th>
<th>year</th>
<th>start</th>
<th>stop</th>
<th>Statin use</th>
<th>ID</th>
<th>start</th>
<th>stop</th>
<th>Statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OS</td>
<td>0</td>
<td>0.00</td>
<td>3.01</td>
<td>fluvastatin</td>
<td>1</td>
<td>0.00</td>
<td>1.01</td>
<td>fluvastatin</td>
</tr>
<tr>
<td>1</td>
<td>OS</td>
<td>3</td>
<td>3.01</td>
<td>5.94</td>
<td>atorvastatin</td>
<td>1</td>
<td>1.01</td>
<td>5.94</td>
<td>atorvastatin</td>
</tr>
</tbody>
</table>

*Note:* Reported duration of statin use was 1 and 2 years at baseline and year 3, respectively.

*Note:* Lipitor use nearly tripled from baseline to Year 1

### Example #2

<table>
<thead>
<tr>
<th>ID</th>
<th>study</th>
<th>year</th>
<th>start</th>
<th>stop</th>
<th>Statin use</th>
<th>ID</th>
<th>start</th>
<th>stop</th>
<th>Statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CT</td>
<td>0</td>
<td>0.00</td>
<td>1.01</td>
<td>lovastatin</td>
<td>2</td>
<td>0.00</td>
<td>1.01</td>
<td>lovastatin</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>1</td>
<td>1.01</td>
<td>2.98</td>
<td>lovastatin</td>
<td>2</td>
<td>1.01</td>
<td>1.98</td>
<td>lovastatin</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>3</td>
<td>2.98</td>
<td>8.78</td>
<td>lovastatin</td>
<td>2</td>
<td>1.98</td>
<td>6.48</td>
<td>lovastatin</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>9</td>
<td>8.78</td>
<td>9.54</td>
<td>lovastatin</td>
<td>2</td>
<td>6.48</td>
<td>6.78</td>
<td>out-of-date med</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>9</td>
<td>6.78</td>
<td>9.54</td>
<td>lovastatin</td>
<td>2</td>
<td>6.78</td>
<td>9.54</td>
<td>lovastatin</td>
</tr>
</tbody>
</table>

*Note:* Reported duration of statin use was 4, 5, 7 and 8 years at baseline, years 1, 3 and 9, respectively.

Follow-up censored during period medication is out of date. Participant is allowed to re-enter risk-set with collection at Year 9.

HR=0.78(0.71, 0.86); p< 0.001

Wang (2016)
## Medications and Supplements

<table>
<thead>
<tr>
<th>Description</th>
<th>Study</th>
<th>One row per</th>
<th>Collected</th>
<th>Data Dictionary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 43 - Hormone Use</td>
<td>CT+OS</td>
<td>Participant</td>
<td>Baseline</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 44 - Current Medications</td>
<td>CT+OS</td>
<td>Medication</td>
<td>Baseline, Main</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 45 - Current Supplements</td>
<td>CT+OS</td>
<td>Form</td>
<td>Baseline, Main</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 150 - Hormone Use Update WHI Extension</td>
<td>HT</td>
<td>Form</td>
<td>Ext1</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 153 - Medication and Supplement Inventory: Barriers (WHI Extension)</td>
<td>CT+OS</td>
<td>Form</td>
<td>Ext1, Ext2</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 153 - Medication and Supplement Inventory: Medications (WHI Extension)</td>
<td>CT+OS</td>
<td>Medication</td>
<td>Ext1, Ext2</td>
<td>PDF</td>
</tr>
<tr>
<td>Form 154 - Breast Health Supplement to the Medication Inventory (WHI Extension)</td>
<td>CT+OS</td>
<td>Participant</td>
<td>Ext1</td>
<td>PDF</td>
</tr>
</tbody>
</table>
Conclusions

- WHI medication use data is a valuable unique resource
- Differential collection frequency between CT & OS
- Collection schedule, cohort and method changed during the extension periods
- Beware of temporal trends and account for out-of-date medications
Resources

- WHI SharePoint
  - Medications and supplements
  - Observational Analyses of Medication Use
  - Approximations of Medication Use in WHI Cohorts
  - helpdesk@WHI.org

- WHI and other publications
  - Manson JE, Shufelt CL, Robins JM. The Potential for Postrandomization Confounding in Randomized Clinical Trials. JAMA. 2016 Jun 7;315(21):2273-4