ENGELBERG CENTER for Health Care Reform at BROOKINGS

Sentinel Initiative Public Workshop

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Developing a PROMPT Surveillance Plan

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MINI-SENTINEL SURVEILLANCE PLAN

MINI-SENTINEL PROSPECTIVE OBSERVATIONAL MONITORING PROGRAM TOOLS (PROMPT), RIVAROXABAN SURVEILLANCE

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Scientific Lead Team

Methods and Analytic Decisions

Feasibility assessment, module selection, comparators, outcome and exposure definitions, parameter settings, alerting rules, etc.

Scientific Lead Team and MSOC

Data Partners

Cohort ID, Extraction & Formatting

Self Controlled (SC):

Cohort - PS Matched (based on MP3)

Cohort - Regression GEE

Cohort - Regression IPTW

SC Format

PS Cohort Format

GEE Format

IPTW Format

MSOC and Leads

Analysis

Alerting

Reporting

SC Analysis Code

PS Analysis Code

GEE Analysis Code

IPTW Analysis Code

Continuous binomial maxSPRT

Group Sequential Unifying Family

Group Sequential Unifying Family

SC Reporting

PS Reporting

GEE Reporting

IPTW Reporting

Scientific Lead Team

Review and Interpretation

Review report and decide on next steps

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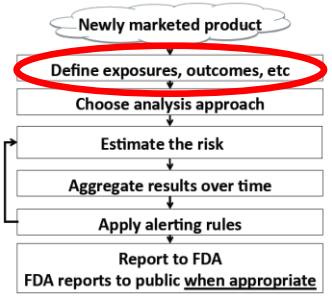
Methods and Analytic Decisions

Feasibility assessment, module selection, comparators, outcome and exposure definitions, parameter settings, alerting rules, etc.



Define exposures, outcomes, etc

→Rivaroxaban PROMPT will conduct surveillance for three health outcomes of interest for rivaroxaban and warfarin

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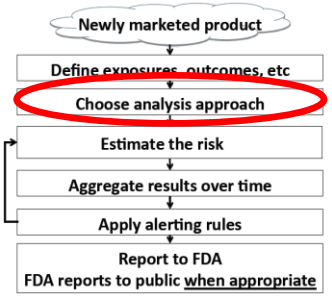


Define exposures, outcomes, etc

↓

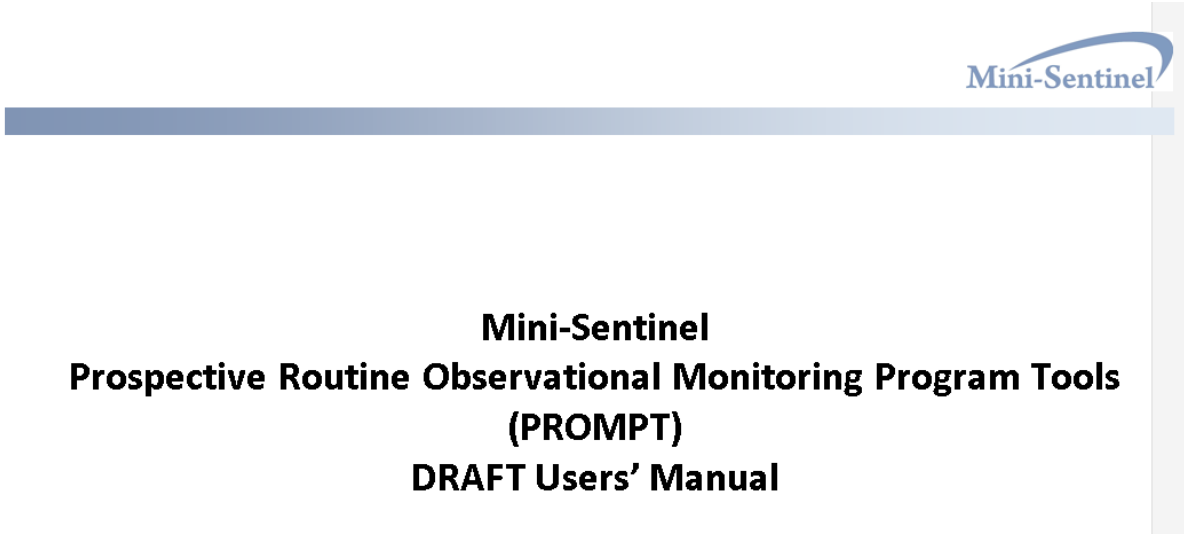
Choose analysis approach

Cohort or self-controlled?

Relative risk? Risk difference?

→Rivaroxaban PROMPT will employ a new user, parallel cohort, propensity-score-matched design

Inputs for Prospective Routine Observational Monitoring Program Tool: cohort matching program



→ Inputs Example: Rivaroxaban Surveillance Plan

ELIGIBILITY INFORMATION

- Enrollment gap – 45 days
- Inclusion/exclusion conditions – Include age 21+ with AF/flutter; Exclude dialysis, kidney transplant, valve disease, joint replacement

EXPOSURE INFORMATION

- Medical product of interest – Rivaroxaban NDCs
- Comparator of interest – Warfarin NDCs

→ Inputs Example: Rivaroxaban Surveillance Plan

EXPOSURE INFORMATION (continued)

- Variable matching ratio
- New user definition
  - 183 day washout
  - Products to define new use – all anticoagulants
- Exposure definition during follow-up
  - Begin follow-up – next day after the index date
  - Treatment episode gap – up to 7 days
  - Episode extension period – 2 days

→ Inputs Example: Rivaroxaban Surveillance Plan

COVARIATE INFORMATION

- Pre-specified covariates
  - Procedures and diagnoses: risk factors for bleeding, ischemic stroke
  - Medications: oral cardiovascular agents, medications that increase bleeding risk, interacting medications
  - Combined comorbidity score
  - Health service utilization variables
- High dimensional propensity score

→ Inputs Example: Rivaroxaban Surveillance Plan

OUTCOME INFORMATION

- Safety Outcomes of Interest –
  - GI bleeding
  - Intracranial hemorrhage
  - Ischemic stroke
- Outcome washout –
  - outcome of interest allowed prior to index date

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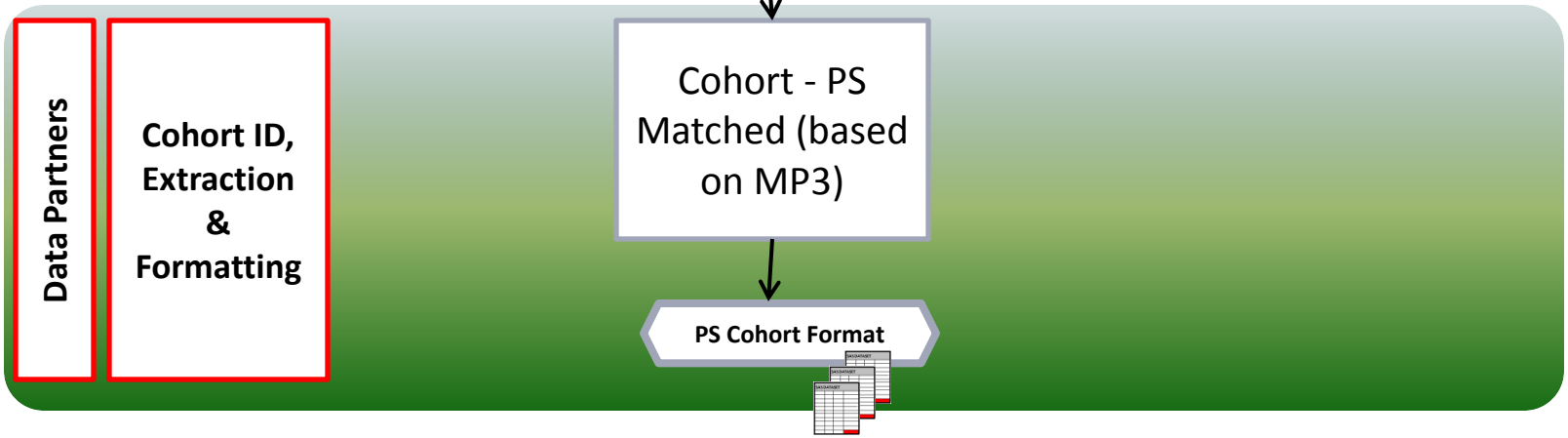
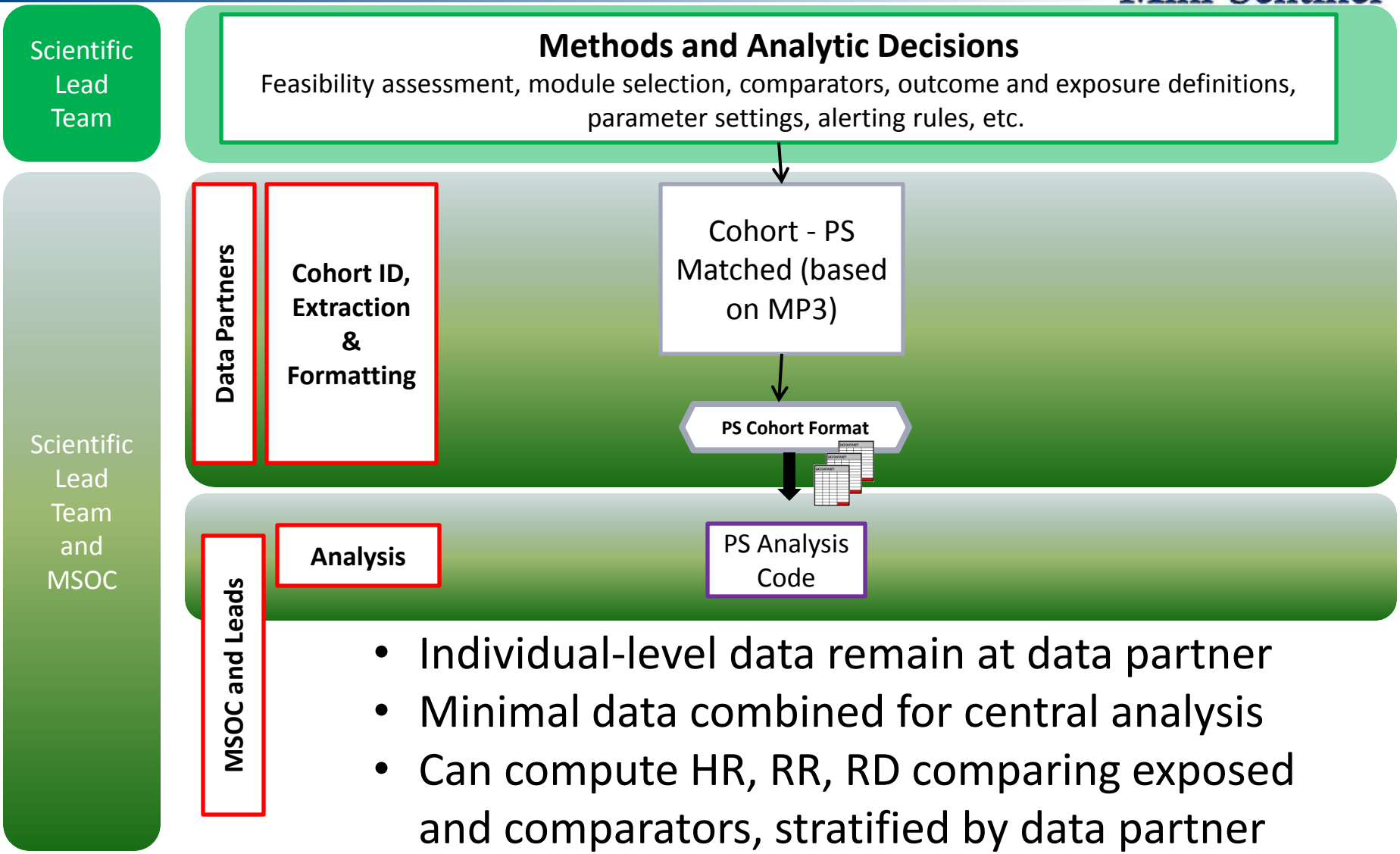


Data extraction capabilities: Substantial flexibility in defining exposures and outcomes, exposure windows, washout period, minimum exposures, blackout periods, etc.



- Individual-level data remain at data partner
- Minimal data combined for central analysis
- Can compute HR, RR, RD comparing exposed and comparators, stratified by data partner

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PS Cohort Format

MSOC and Leads

Analysis

PS Analysis Code

Alerting

Continuous binomial maxSPRT;
'Hand-cranked' survival data option (group; unifying; Wald; large samples)

→ Analysis Inputs: Rivaroxaban Surveillance Plan

SEQUENTIAL ANALYSIS INFORMATION

- Group sequential design, 5 looks
- A Cox regression model
- Sample size at final look – See Table

→ Analysis Inputs: Rivaroxaban Surveillance Plan

Number of rivaroxaban new-users needed at final look

MINIMUM DETECTABLE RELATIVE RISK	INTRACRANIAL HEMORRHAGE	GASTRO-INTESTINAL BLEEDING	ISCHEMIC STROKE
1.5	17,073	11,951	7,030
2.0	4,961	3,473	2,043
3.0	1,536	1,075	632

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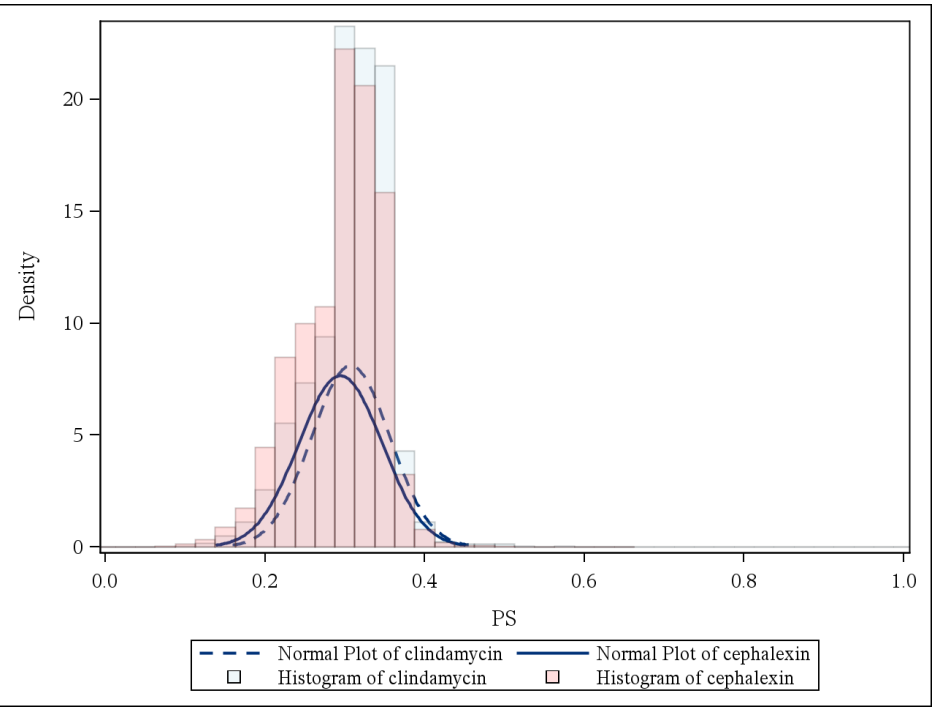
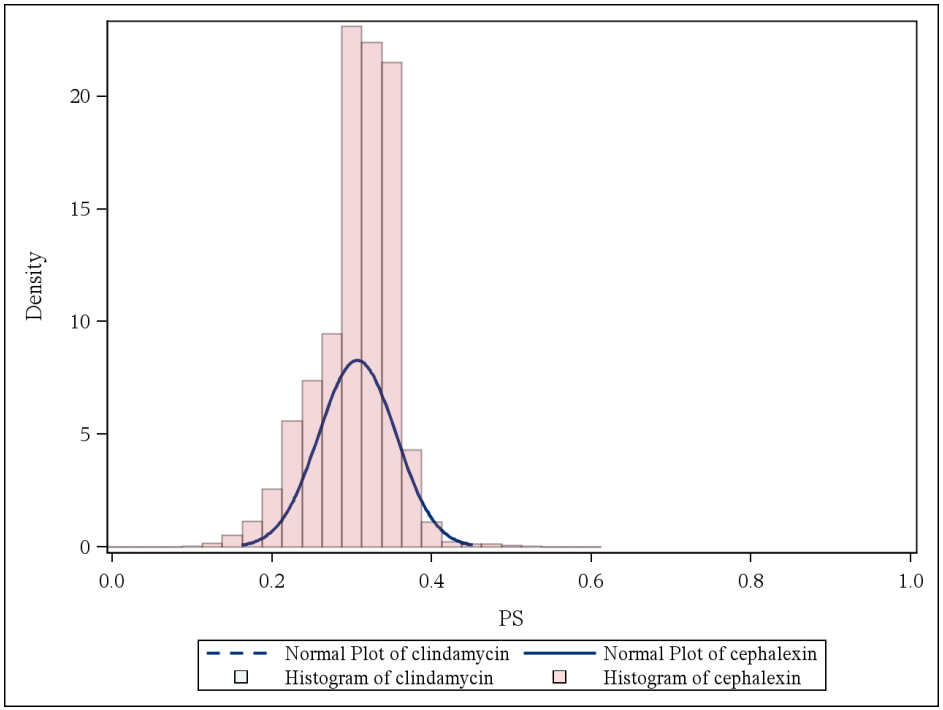
PS Reporting

Matched Cohort: Diagnostic output

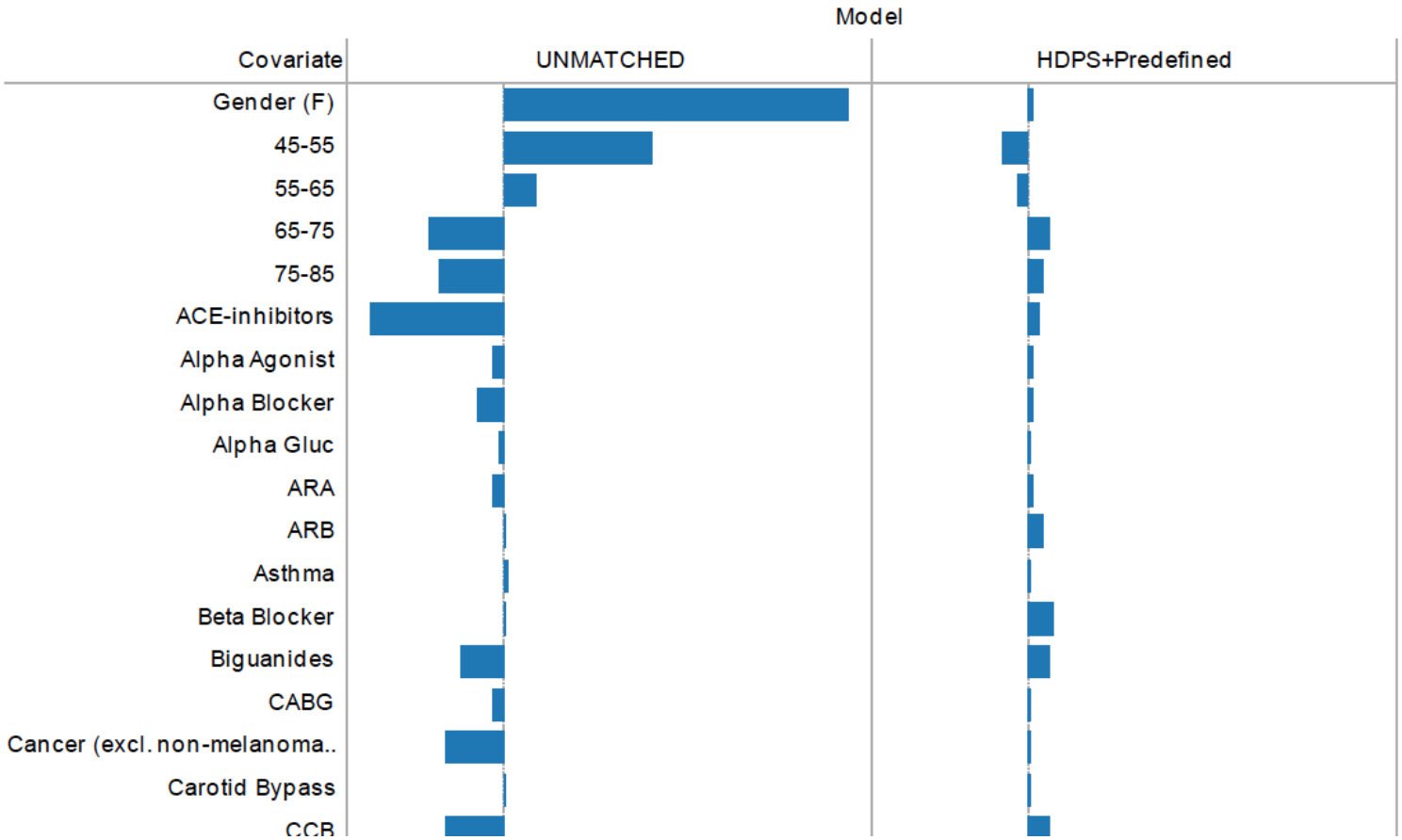
Histogram of PS, Unmatched Cohort



Histogram of PS, Matched Cohort



Diagnostics: Balance before/after matching



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PS Reporting

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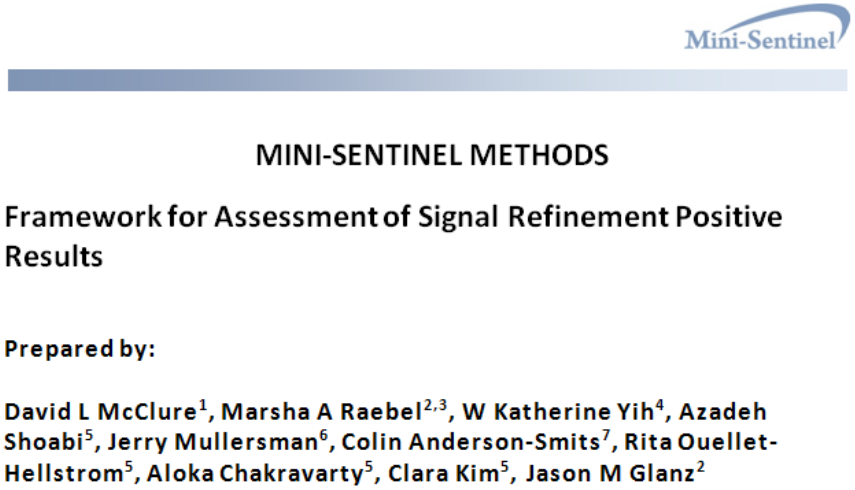
Review and Interpretation

Review report and decide on next steps

What happens when we find something?

- Prompt, pre-planned product-specific assessment of positive signal (or in the absence of signal)
- Examples of post-monitoring follow-up activities:
  - Data checks, analytic code checks
  - Subgroup analyses
  - Adjust for additional confounders
  - Test against other comparators
  - Vary population, O, or E definitions
  - Medical chart validation of cases
  - Quantitative bias analysis
  - Detailed epidemiologic investigation to assess causality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MINI-SENTINEL METHODS

Framework for Assessment of Signal Refinement Positive Results

Prepared by:

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