

**OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP**

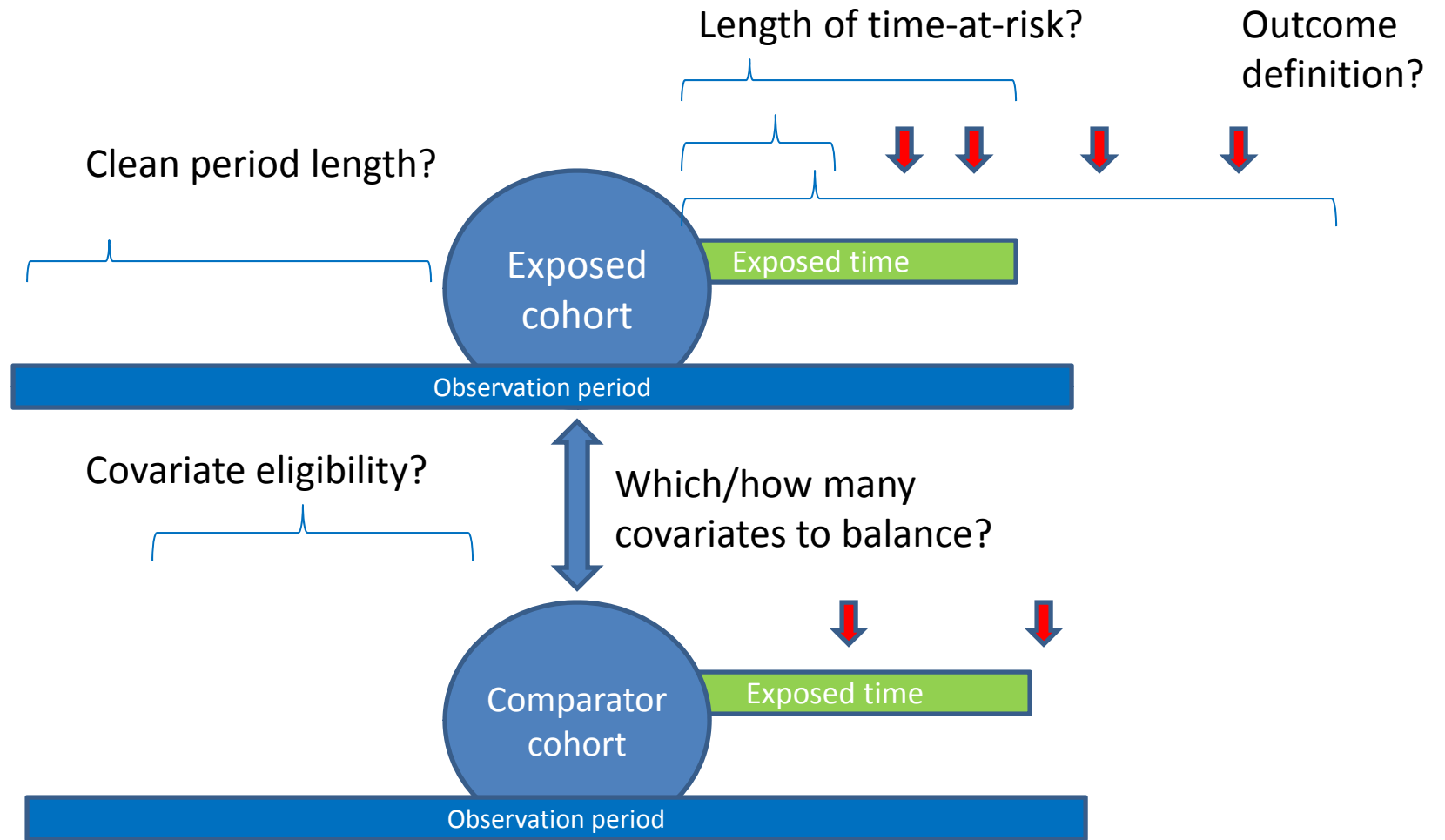
**Impact of Observational Analysis
Design: Lessons from the OMOP
Experiment**

Patrick Ryan, David Madigan
April 14, 2011

Active surveillance methods under evaluation in OMOP experiment

Method name	Contributor	Release date	Parameter combinations
Disproportionality analysis			
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10	112
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10	84
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10	6
Case-based methods			
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10	64
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10	32
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10	24
Case-control surveillance (CCS)	Lilly	2-May-10	48
Case-crossover (CCO)	University of Utah	1-Jun-10	48
Exposure-based methods			
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10	162
High-dimensional propensity score (HDPS)	Columbia	6-Aug-10	144
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10	160
Sequential testing methods			
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10	144
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10	144

Exploration of test cases within inception cohort design



Exclusion criteria:
Indications
Contraindications

Which active
comparator?

Propensity score adjustment strategy?
Stratification
Multivariate adjustment

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,¹ Gabriela Czanner, statistician,¹ Gillian Reeves, statistical epidemiologist,¹ Joanna Watson, epidemiologist,¹ Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,² Valerie Beral, professor of cancer epidemiology¹

BMJ 2010; 341:c4444

Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period.

BMJ study design choices

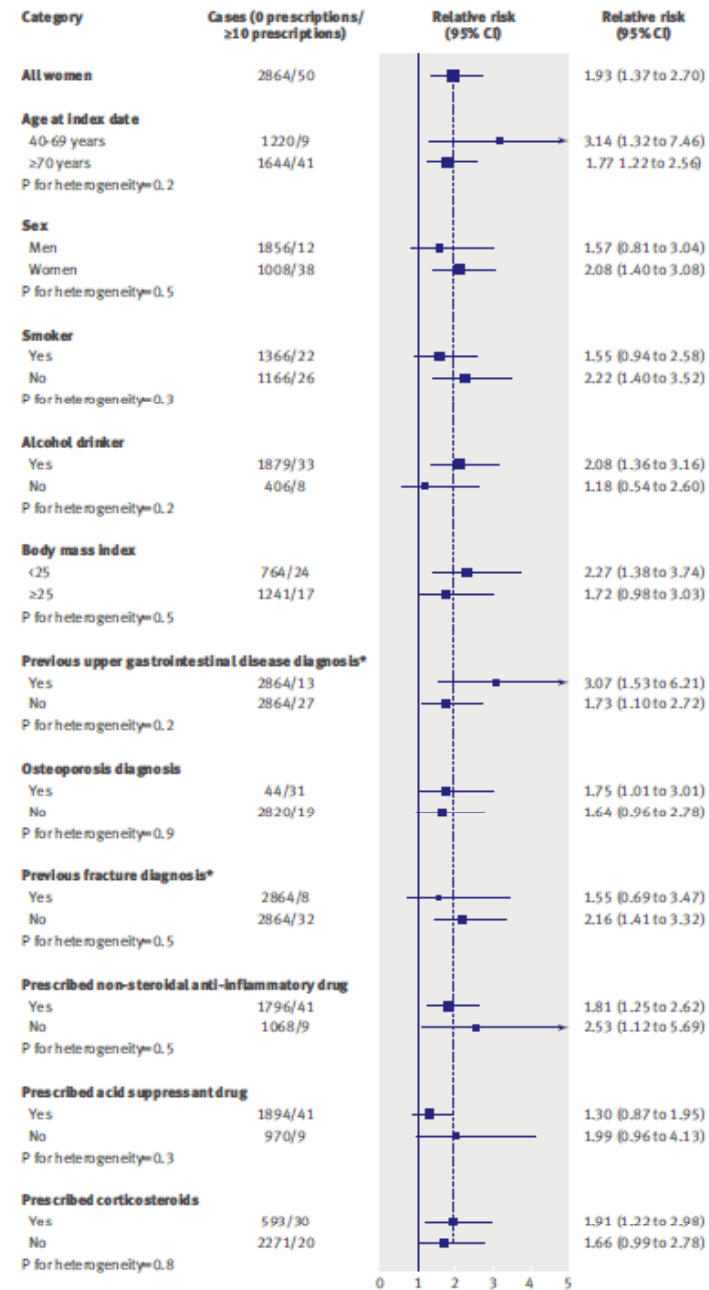
- Data source: General Practice Research Database
- Study design: Nested case-control
- Inclusion criteria: Age > 40
- Case: cancer diagnosis between 1995-2005 with 12-months of follow-up pre-diagnosis
- 5 controls per case
- Matched on age at index date, sex, practice, observation period prior to index
- Exposure definition: ≥ 1 prescription during observation period
- “RR” estimated with conditional logistic regression
- Covariates: smoking, alcohol, BMI before *outcome* index date
- Sensitivity analyses:
 - exposure = 2+ prescriptions
 - covariates not missing
 - time-at-risk = >1 yr post-exposure
- Subgroup analyses:
 - Short vs. long exposure duration
 - Age, Sex, smoking, alcohol, BMI
 - Osteoporosis or osteopenia
 - Fracture pre-exposure
 - Prior diagnosis of Upper GI dx pre-exposure
 - NSAID, corticosteroid, H2blocker, PPI utilization pre-exposure

BMJ Results

Table 2 | Relative risks (RRs) and 95% confidence intervals (CIs) for bisphosphonates

Oral bisphosphonates	Oesophagus		RR† (95% CI)
	Prescriptions*	Cases/controls	
Not prescribed	NA	2864/14 376	1.00
Prescribed	13.6/2.4	90/345	1.30 (1.02 to 1.66)
No of prescriptions:			
1-9	3.6/1.0	40/214	0.93 (0.66 to 1.31)
≥10	21.6/3.5	50/131	1.93 (1.37 to 2.70)
Estimated duration of use‡:			
≤1 year	4.9/0.3	31/155	0.98 (0.66 to 1.46)
1-3 years	13.0/2.0	26/114	1.12 (0.73 to 1.73)
≥3 years	22.2/4.6	33/76	2.24 (1.47 to 3.43)

NA=not applicable.
*Prescriptions of bisphosphonates in cases; reported as mean number/mean year
†All relative risks adjusted for smoking status, alcohol intake, and body mass index
‡Time between first and last prescription.



Relative risks of incident oesophageal cancer in people with ≥10 prescriptions for oral bisphosphonates, compared with those with no prescriptions, by various factors. Relative risks adjusted for smoking status, alcohol intake, and body mass index, as appropriate. *Diagnosis before prescription of bisphosphonates: analyses restricted to those with ≥12 months' observation before first bisphosphonate prescription

JAMA[®]

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

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Context Use of oral bisphosphonates has increased dramatically in the United States and elsewhere. Esophagitis is a known adverse effect of bisphosphonate use, and recent reports suggest a link between bisphosphonate use and esophageal cancer, but this has not been robustly investigated.

Objective To investigate the association between bisphosphonate use and esoph-

JAMA 2010; 304(6): 657-663

Conclusion

of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer. the use

JAMA study design choices

- ✓ Data source: General Practice Research Database
- ✗ Study design: Cohort
- ✓ Inclusion criteria: Age > 40
- ✗ Exclusion criteria: Cancer diagnosis in 3 years before index date
- ✓ Exposed cohort: Patients with ≥ 1 prescription between 1996-2006 **1995-2005 in BMJ**
- ✗ “Unexposed” cohort: 1-to-1 match with exposed cohort **Match exposure vs.**
- ✓ Matched on year of birth, sex, practice **Not observation length outcome status; not 5-to-1**
 - “HR” estimated with Cox proportional hazards model
- ✗ Time-at-risk: >6mo from index date **Time-at-risk is ‘between’ two definitions used in BMJ: All time post-exposure and >1yr after index**
- ✓ Covariates: **Different index date**
 - Smoking, alcohol, BMI before *exposure* index date **BMJ didn’t stratify by hormone therapy**
 - Hormone therapy, NSAIDs, H2blockers, PPIs
- Sensitivity analyses:
 - Excluding people that were in both exposed and unexposed cohorts
 - Exclude patients with missing confounders (not reported)
- Subgroup analyses:
 - Low vs. medium vs. high use, based on defined daily dose
 - Alendronate vs. nitrogen-containing bisphosphonates vs. non-nitrogen-containing bisphosphonates

JAMA Results

Table 3. Esophageal (Only) Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

Bisphosphonate Category	Bisphosphonate		Control		Risk			
	Cases	Person-Years	Cases	Person-Years	Unadjusted		Adjusted ^a	
					HR (95% CI)	P Value	HR (95% CI)	P Value
Any bisphosphonate Prescribed	79	165 400	72	163 480	1.08 (0.79-1.49)	.63	1.07 (0.77-1.49)	.67
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
183	51	104 676	49	104 104	1.04 (0.70-1.53)	.86	1.05 (0.70-1.57)	.82
365	31	73 364	35	73 170	0.88 (0.55-1.43)	.62	0.92 (0.56-1.51)	.74
730	22	40 326	22	40 492	1.00 (0.56-1.81)	.99	0.98 (0.53-1.81)	.95
1095	15	22 813	14	22 891	1.08 (0.52-2.23)	.84	1.01 (0.48-2.12)	.99
Total bisphosphonate intake during follow-up (in DDDs/d) ^c								
Low (0-<0.24)	35	62 922	27	63 648	1.31 (0.80-2.17)	.29	1.24 (0.74-2.09)	.41
Medium (≥0.24-<0.89)	24	58 162	23	55 334	0.98 (0.55-1.74)	.94	1.03 (0.57-1.86)	.92
High (≥0.89)	20	44 316	22	44 497	0.91 (0.50-1.67)	.78	0.90 (0.48-1.68)	.74
Nitrogen-containing bisphosphonates								
First prescribed	44	106 480	47	106 412	0.94 (0.62-1.41)	.75	0.96 (0.63-1.47)	.86
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
365	30	70 251	34	69 935	0.88 (0.54-1.44)	.61	0.93 (0.56-1.54)	.78
730	22	39 022	22	39 187	1.01 (0.56-1.82)	.99	0.98 (0.53-1.80)	.95
Alendronate								
First prescribed	33	81 369	42	80 837	0.78 (0.50-1.23)	.29	0.77 (0.48-1.23)	.27
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
365	22	52 308	31	51 741	0.70 (0.41-1.21)	.20	0.68 (0.39-1.19)	.18
730	19	28 898	21	28 904	0.91 (0.49-1.68)	.75	0.85 (0.45-1.61)	.62
Non-nitrogen-containing bisphosphonates								
First prescribed	35	58 920	25	57 068	1.35 (0.81-2.25)	.25	1.25 (0.73-2.12)	.37

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio.

^aAdjusted for body mass index, alcohol, smoking, hormone therapy prescription (before index date), nonsteroidal anti-inflammatory drug prescription (before index date), Barrett esophagus diagnosis (before index date), gastroesophageal reflux disease diagnosis (before index date), H₂ receptor antagonist prescription (before index date), and proton pump inhibitor prescription (before index date).

^bPerson-years and cancer cases occurring after the date of specified prescriptions received for each bisphosphonate cohort member and their matched control. Daily divided dose equivalents: 183 DDDs are equivalent to a 6-month supply; 365 DDDs to a 1-year supply; 730 DDDs to a 2-year supply; and 1095 DDDs to a 3-year supply.

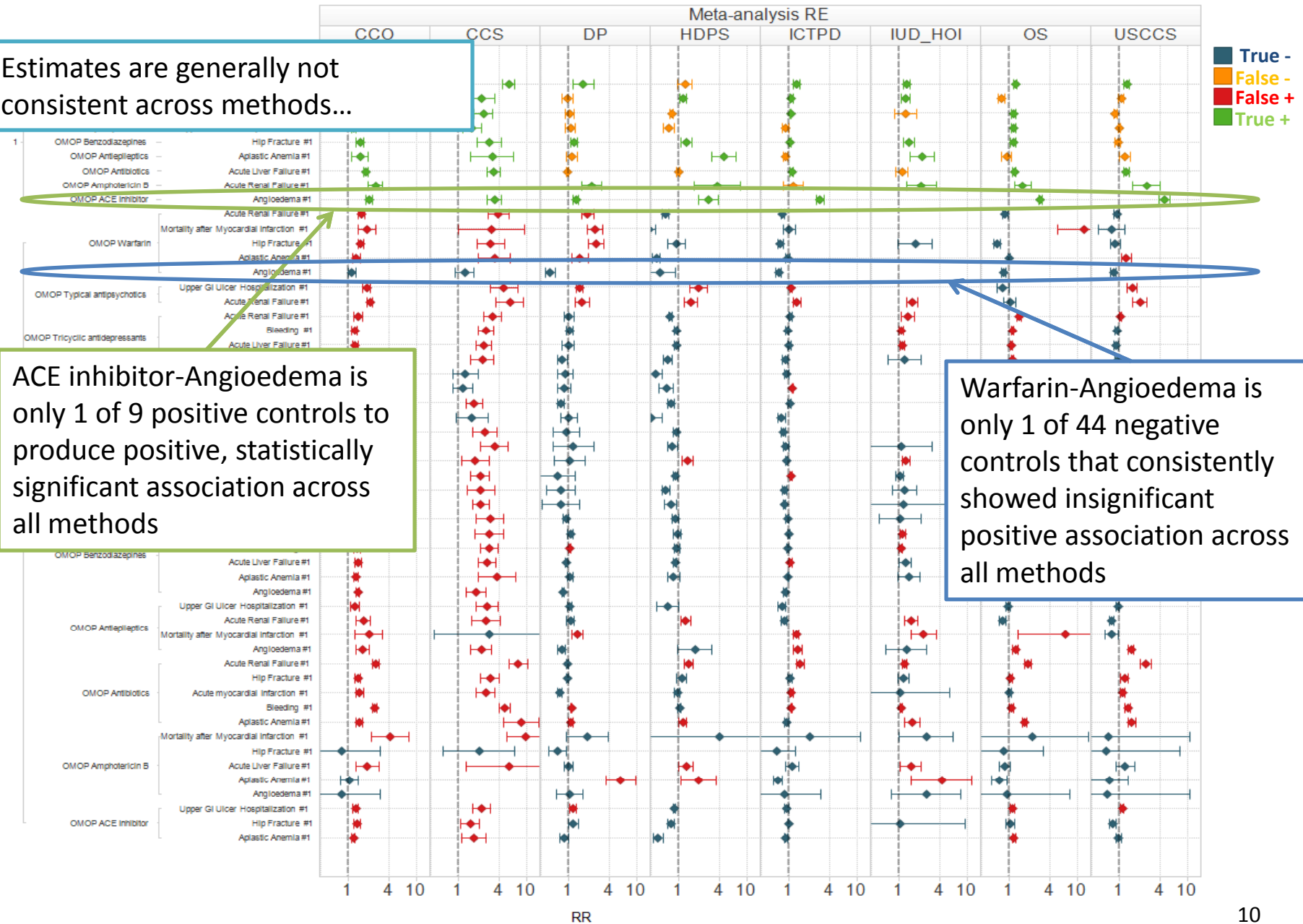
^cIn bisphosphonate cohort (see "Methods" for details of selection of cohorts).

Distribution of estimates across all drug-outcome pairs

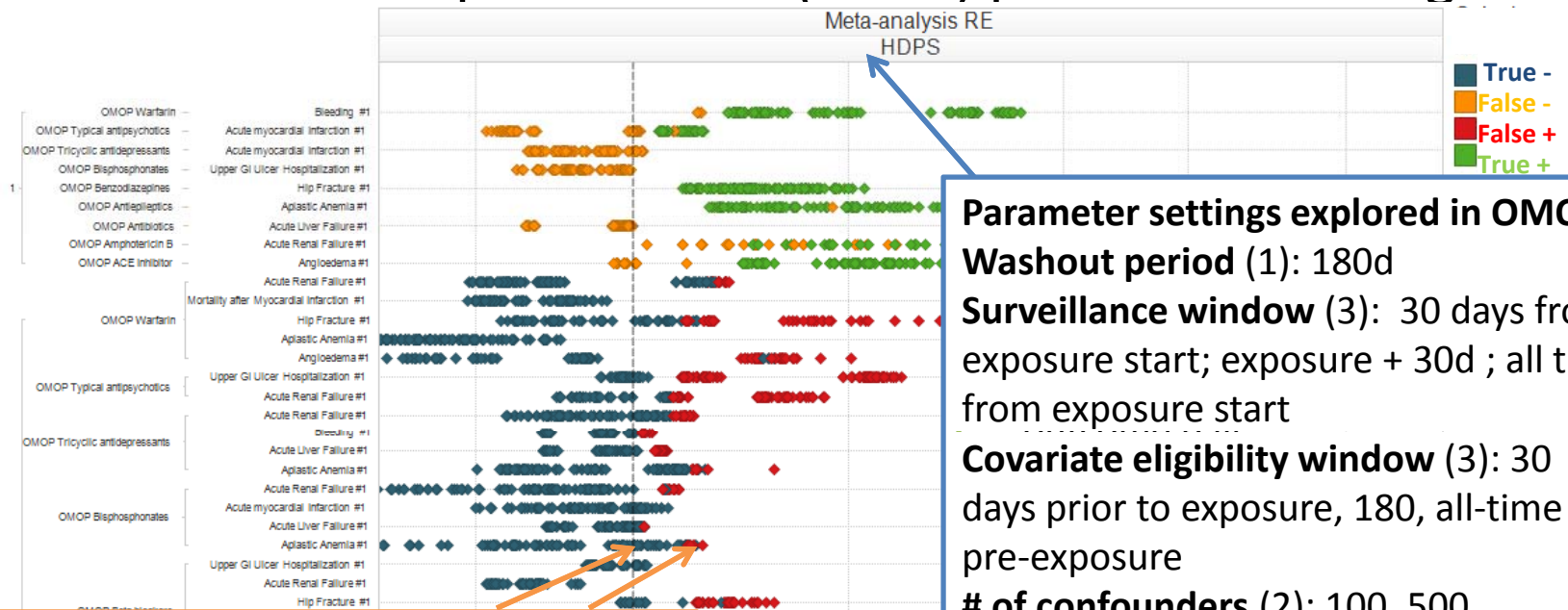
Estimates are generally not consistent across methods...

ACE inhibitor-Angioedema is only 1 of 9 positive controls to produce positive, statistically significant association across all methods

Warfarin-Angioedema is only 1 of 44 negative controls that consistently showed insignificant positive association across all methods



Range of estimates across high-dimensional propensity score inception cohort (HDPS) parameter settings



- When using all-time pre-exposure as covariate eligibility window, 100 confounders, propensity stratification with 20 strata, and comparator class of all drugs with same indication not in same class...
- HDPS produces significant, positive effect for bisphosphonates-aplastic anemia when surveillance window is 'all time post-exposure' (RR=1.25)...
- ...but shows no effect when time-at-risk defined by exposure length + 30 days (RR=1)

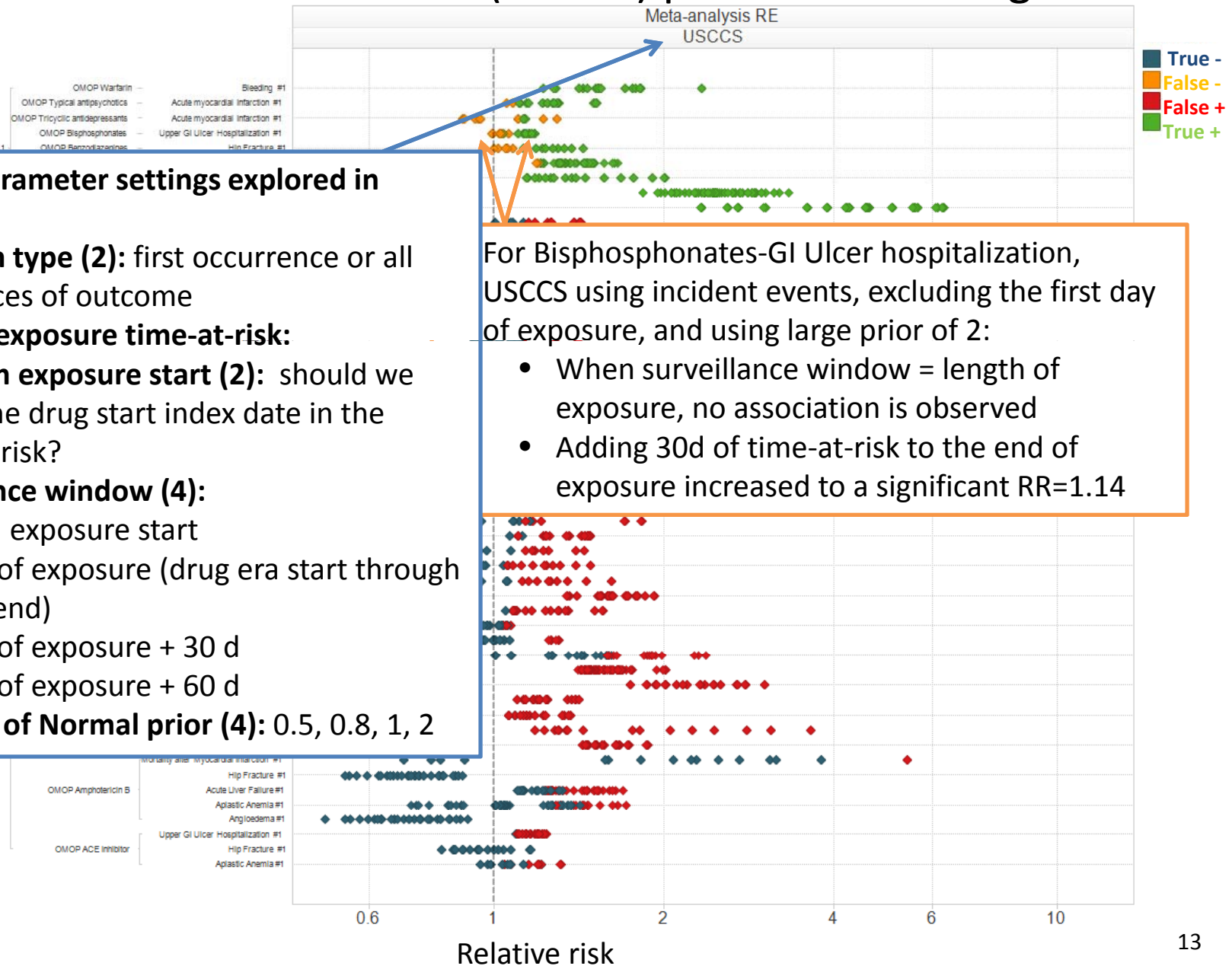
Parameter settings explored in OMOP:

- Washout period (1):** 180d
- Surveillance window (3):** 30 days from exposure start; exposure + 30d ; all time from exposure start
- Covariate eligibility window (3):** 30 days prior to exposure, 180, all-time pre-exposure
- # of confounders (2):** 100, 500 covariates used to estimate propensity score
- Propensity strata (2):** 5, 20 strata
- Analysis strategy (3):** Mantel-Haenszel stratification (MH), propensity score adjusted (PS), propensity strata adjusted (PS2)
- Comparator cohort (2):** drugs with same indication, not in same class; most prevalent drug with same indication, not in same class

HDPS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Time-at-risk surveillance window (30d from exposure start, exposure length + 30d, all time post-exposure start)
 - Choice of comparator (all drugs with same indication but in different class, one drug with same indication but different class)
- Effect estimates are less sensitive for:
 - Covariate eligibility window (30d, 180d, all time pre-exposure)
 - Number of covariates (100, 500)
 - Propensity score adjustment strategy (stratification with 5 or 20 strata, multivariate regression with strata categories, regression with PS as covariate)

Range of estimates across univariate self-controlled case series (USCCS) parameter settings



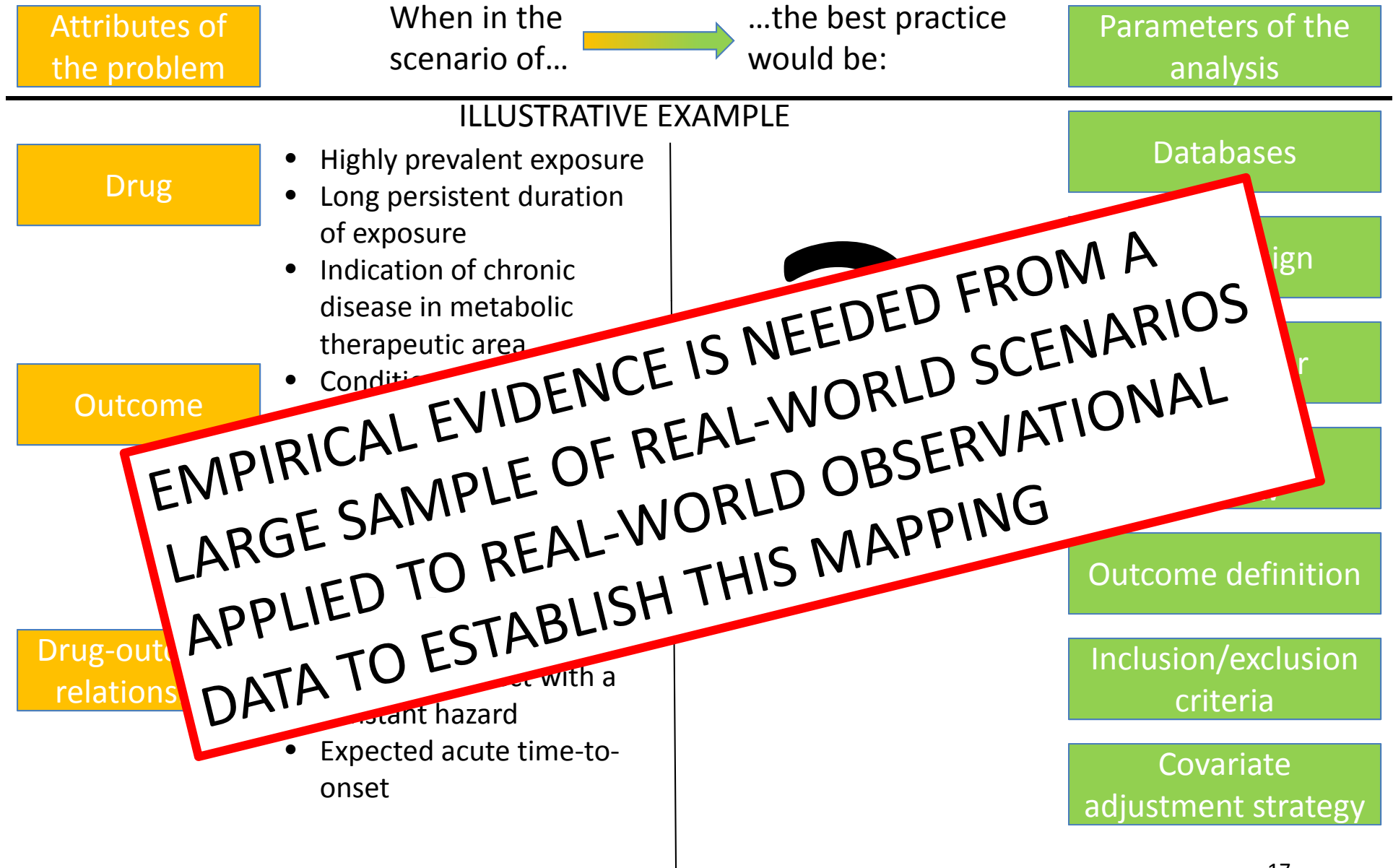
USCCS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Whether to include the exposure start date as exposed time-at-risk: including day 0 produced higher estimates than excluding day 0 for many pairs
 - Exposed time-at-risk surveillance window
 - Length of exposure
 - Length of exposure + 30d
 - Length of exposure + 60d
 - 30d from exposure start
 - NOTE: Time ‘unexposed’ = Total observation period – time exposed
- Effect estimates are less sensitive for:
 - Use of first occurrence vs. all occurrences of events
 - Precision of the prior (0.5, 0.8, 1, 2)

CCS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Number of controls per case (4, 100)
 - 100 controls generated higher estimates than 4 controls for many drug-outcome pairs
 - Whether to match on race and location
 - Matching on race and location generated lower estimates than not matching for many drug-outcome pairs
 - Time-at-risk surveillance window (30d post-exposure, all-time post-exposure start)
 - 30d post-exposure generated higher estimates than all-time post-exposure for many drug-outcome pairs
- Effect estimates are less sensitive:
 - Lead time (30d, 91d, 183d)
 - Follow-up time (30d, 180d)

Mapping clinical problems to analytical solutions



EMPIRICAL EVIDENCE IS NEEDED FROM A LARGE SAMPLE OF REAL-WORLD SCENARIOS APPLIED TO REAL-WORLD OBSERVATIONAL DATA TO ESTABLISH THIS MAPPING

Establishing robust practice through empirical research

- For ‘risk identification’, many of the attributes of drug-outcome relationship may not be known a priori, so systematic analysis requires comprehensive exploratory framework
- Current data suggest need for systematic sensitivity analysis
- A viable best practice may be:
“Don’t use observational data for this scenario, due to lack of evidence that a reliable estimate can be obtained”
- Further empirical research needed to have more complete understanding of operating characteristics and sensitivities before widespread adoption