Risk benefit analysis using administrative claims data: Some considerations

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Outline

- Post-marketing benefit risk evaluation.
- Specific considerations in use of claims/EHR data.
- Preparing for post-marketing safety evaluation.

Complete understanding of benefit risk for any drug is an aspirational goal not likely achievable

- Ideally, we would want to know the likelihood of (causal) benefits and harms from exposing each individual to a drug.
- In the absence, we use the current evidence to ensure a positive benefit risk in the margins of a target population.
- There are consequences of improper or inadequate characterization of this target population.

Decision making based on sub-optimal benefit risk evidence has significant consequences

- Termination of development programs that may have led to benefit.
- Approvals OR denials that lead to patient harm by exposure or by lack of access, respectively.
- Misuse of resources, misappropriation of investments.

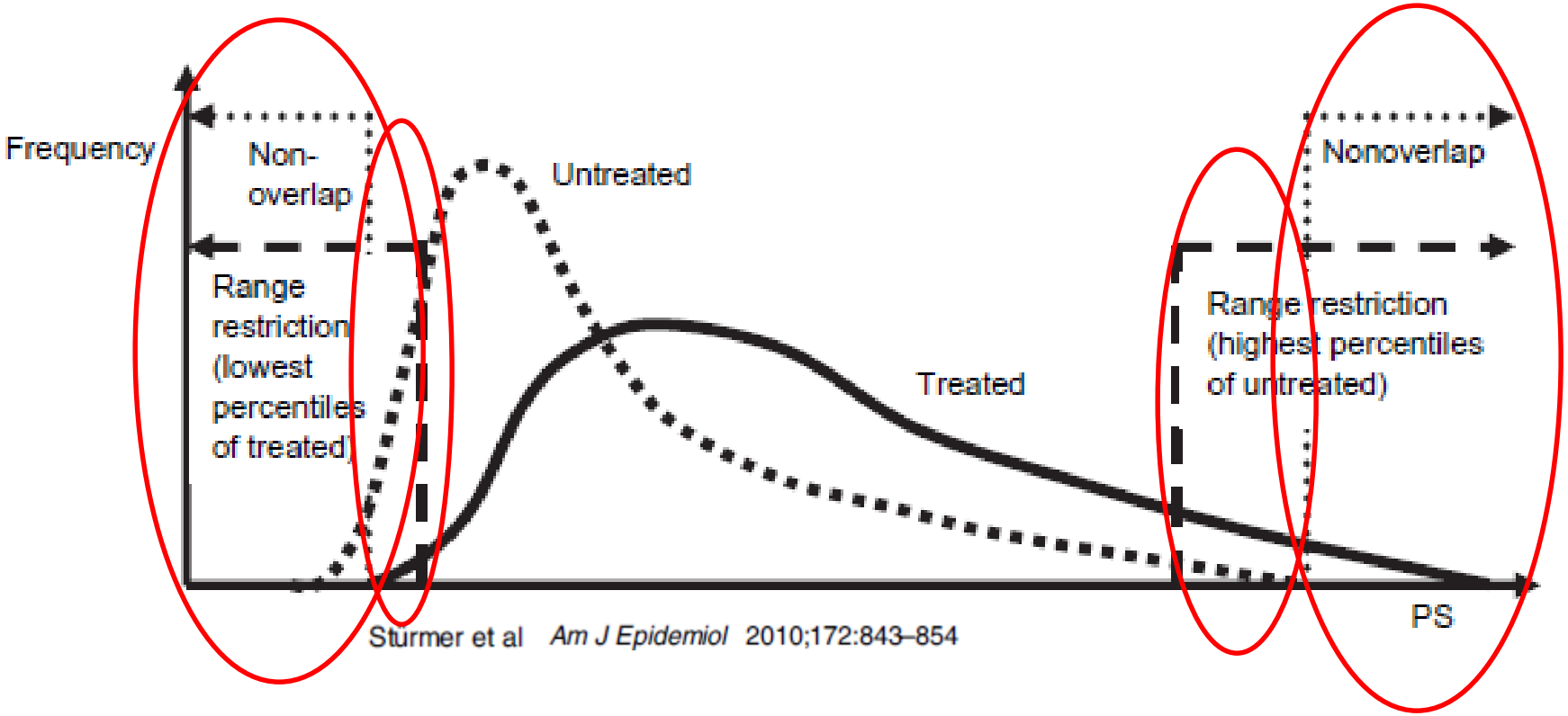
Much of the imperative for post-marketing evidence concerns risk identification and not benefit

- Regulatory approval often based on favorable risk benefit profile during the dev. program (efficacy and safety).
- Requisite real-world studies (PMCs, PASS) often have a primary safety objective: Effectiveness is "assumed"
- Active, real-time monitoring of risk takes place without such a parallel for evaluating benefit.
- To maximize societal value, effort should be taken to ensure the BR profile includes the best evidence on both sides of the equation.

The many ways to use the propensity score…

- Can be used to describe real-world clinical practice.
- Can be used as a covariate to adjust for confounding.
- Can be used as a matching variable or stratification variable (e.g. within some caliper of the PS or within quintiles).
- Can be used as to build a weight (e.g. inverse probability of treatment weights).

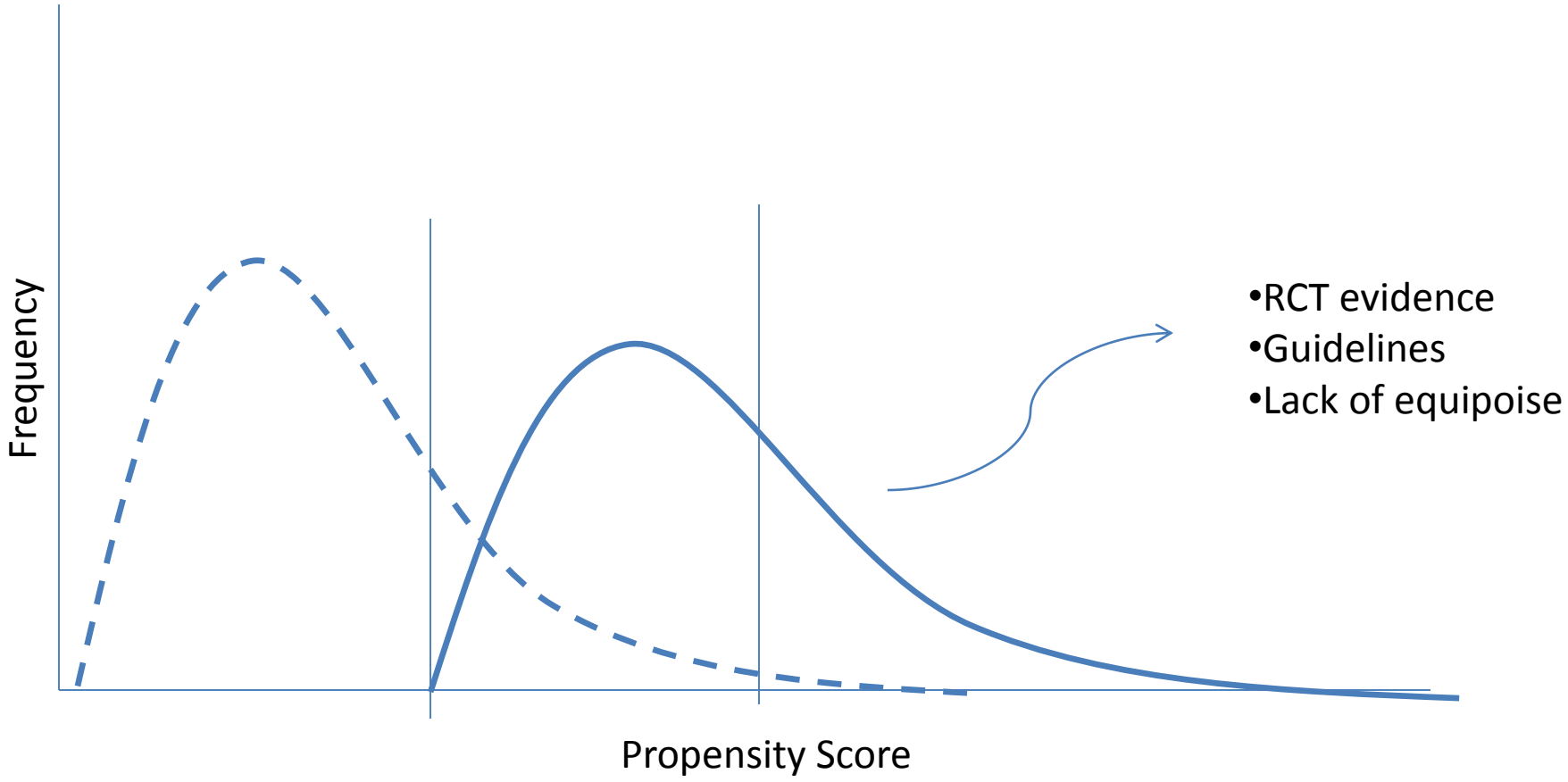
PS distribution is useful in identifying a number of patient groups



What population can we study and how does it affect our interpretation of results

- Always Treated
  - Lack of clinical equipoise, compelling clinical evidence
  - Strict guidelines or formularies
- Always Untreated
  - No presumed benefit/Off-label
  - Contraindicated
- Treated despite low propensity
  - “Unusual” treatment pattern – source of clinical variability
  - Off-label use /inappropriate use
  - Unmeasured confounding (e.g. confounding by frailty – last ditch effort)
- Untreated despite high propensity
  - “Unusual” treatment pattern – source of clinical variability
  - Unmeasured confounding (cost of copay, insurance, confounding by frailty – futility)

Who is in the analysis set?



Study population of patients with “moderate” indication

Extrapolating to those with determinant treatment patterns

- We can not study the effect of treatment among those always treated as there is no exchangeability.
- This will inherently limit our ability to make inferences about the benefit or risk among those often most likely to use a therapy.
- Can estimate RD or NNT though if we make assumptions about homogeneity of the treatment effect from the observed population
- Use data from an earlier time when equipoise existed, given all else is reasonably the same.

Are we more likely to observe risks or benefits in the study population?

Limiting to “moderate indication” may not include patient groups maximally benefiting

- “It is reasonable to assume that treatment is most beneficial for those subjects most suitable for treatment, and this phenomenon may cause different treatment effects across the range of the propensity score. “ (Lunt…Sturmer, AJE, 2009).

Can we identify benefit in claims/EHR data?

- There are significant challenges to identifying clinical risks (see Lanes..Walker AM, PDS 2015) much less benefit.
- Do “benefits” come to clinical attention? What outcomes are most important to patients?
- Interesting application of social media mining, etc.

Epidemiologists within drug development companies are key to proactive and reactive benefit risk evaluation

Discovery → Phase 2 → Phase 3 → Post-approval

Sizing and characterizing the target population

Develop patient profile
Demographics, comorbidities, treatments

Clinical trial development
Feasibility evaluation
- Event rates to drive inclusion/exclusion & power
- Patient mapping for recruitment

Contribute to forecasting & HE
Event rates, transition probabilities, offsets

Phase IV & RWE

- **RW Use & Effectiveness**
- Optimal use, quality metrics & access
- Comp. effectiveness & differentiation

Contribute to Pre-marketing PV & Safety

- Signal evaluation – background rates
- RMP strategy and development
- PV Strategy & development

Prepare for post-marketing PV

- Understand channeling/confounding
- Evaluate RWD needs for safety monitoring
- Algorithm validation, etc for studies

Contribute to post-marketing PV

- Initiate & execute any obs. PMCs/PMRs/PASS
- Signal evaluation
- Proactive benefit risk evaluation
- REMS activities

Evaluating and Communicating Disease Burden & Unmet Need

Partner in medical strategy and publication plan
- Develop an observational research program for disease state
- Publications and communications to clinical community

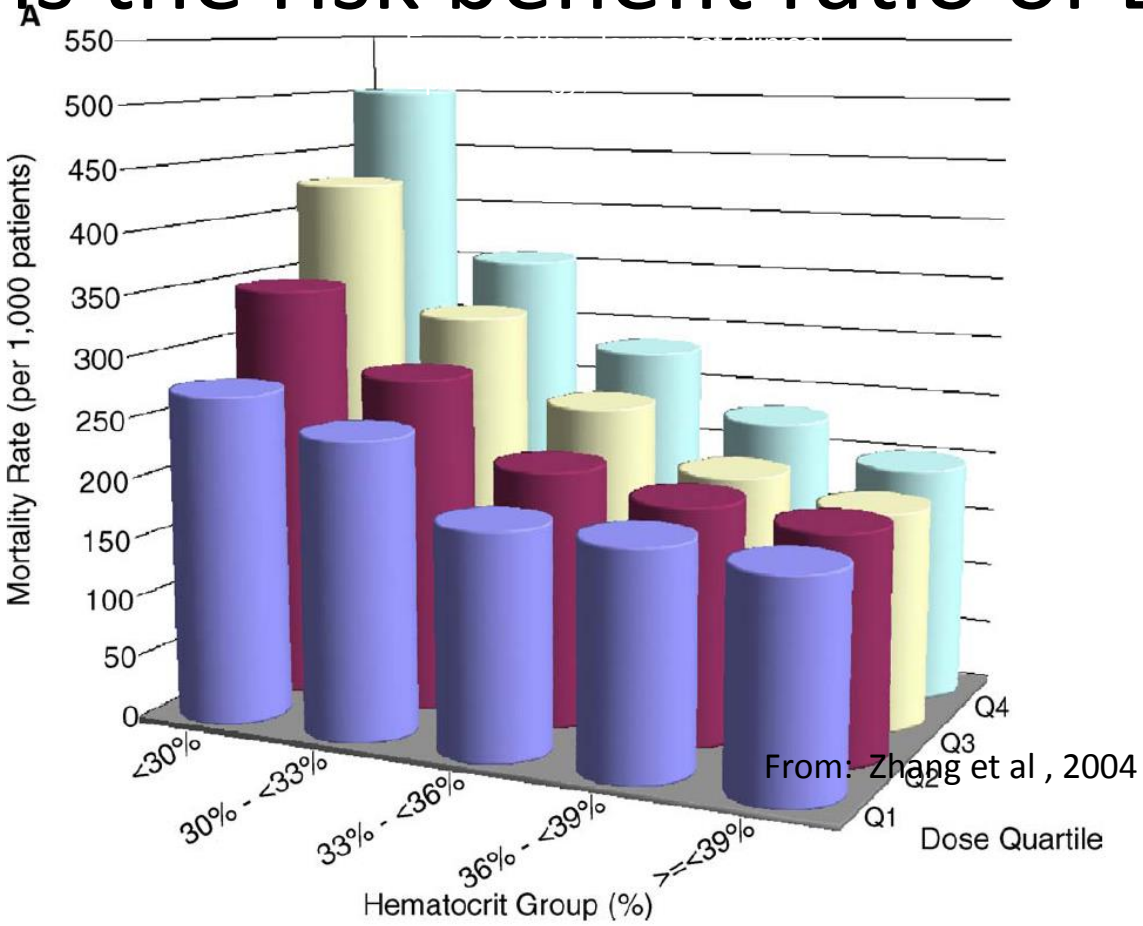
Engagement with OLs, societies

Contribute to BD Activities – Due Diligence

Epidemiologists in BioPharma Companies Have Significant Opportunities to Contribute

- We have the ability to prepare for benefit risk evaluation in the post-marketing setting.
- Understand our target patient population
  - Can we identify them in claims/EHR
  - Are the risks and perhaps benefits able to be measured?
    - Algorithm validation, patient focused research
  - What would a protocol synopsis look like to study risks and benefits?
- Prepare for comparative effectiveness
  - Data sources, funding, internal approvals
  - Channeling, confounding by indication, reasons to initiate treatment, etc can all be elucidated.

A number of studies and reports questions the risk benefit ratio of ESAs



From: Zhang et al , 2004

"The observed association between epoetin dose and survival could also be explained by an unexpected effect of high epoetin doses …..independent of any effect on hematocrit levels."

Relationship between Epoetin Alfa Dose and Mortality: Findings from a Marginal Structural Model

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Treatment Model[a]	Weight Truncation Level, %	Maximum Weight	Zero Dose HR (95% CI)	Epoetin alfa Dose Group			
				Category 1	Category 2, HR (95% CI)	Category 3, HR (95% CI)	Category 4, HR (95% CI)
Simple	2	32	1.69 (1.06, 2.39)	Referent	1.09 (0.92, 1.31)	1.27 (1.02, 1.60)	1.51 (1.08, 1.89)
Case-mix	2	28	1.62 (1.16, 2.09)	Referent	1.09 (0.94, 1.35)	1.24 (1.05, 1.56)	1.49 (1.22, 1.91)
Expanded	2	82	1.56 (0.98, 2.02)	Referent	1.07 (0.91, 1.33)	1.21 (1.00, 1.53)	1.39 (1.08, 1.91)
Simple	1	133	1.71 (1.00, 2.55)	Referent	1.01 (0.83, 1.26)	1.07 (0.89, 1.42)	1.15 (0.94, 1.68)
Case-mix	1	117	1.81 (0.87, 2.51)	Referent	1.02 (0.82, 1.29)	1.11 (0.85, 1.41)	1.21 (0.90, 1.70)
Expanded	1	471	1.72 (0.84, 2.59)	Referent	0.97 (0.79, 1.33)	1.00 (0.81, 1.45)	0.98 (0.76, 1.74)

From: Wang, CJASN, 2010

Near violations of ETA can lead to very large weights

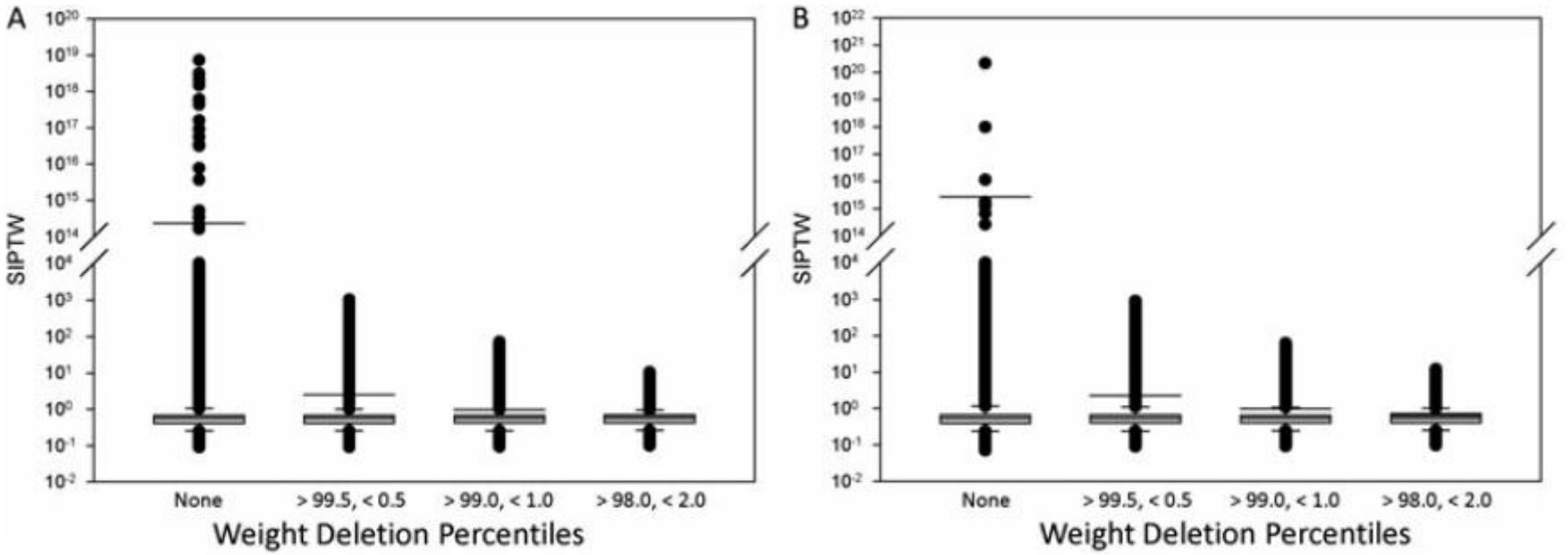
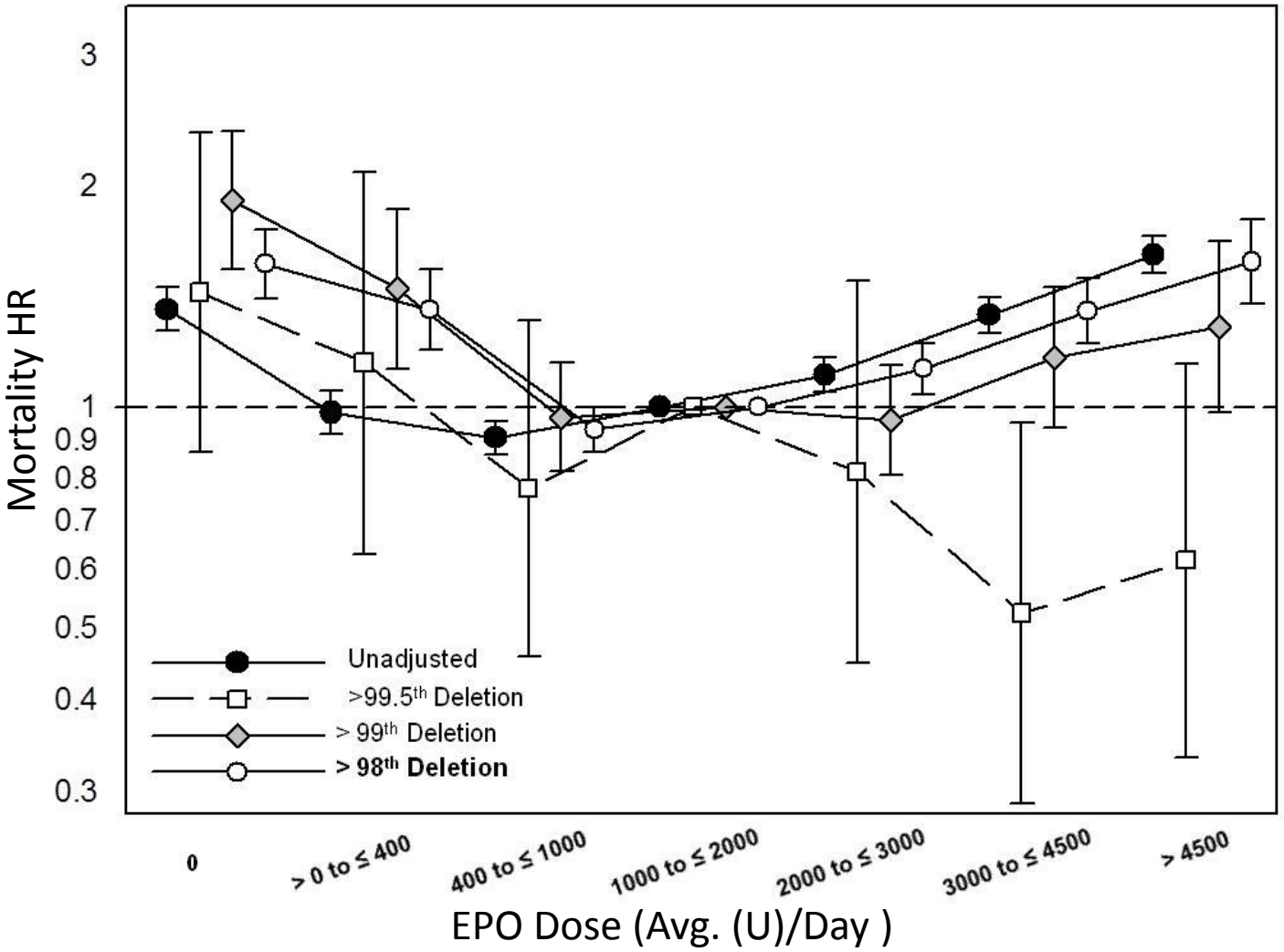


Figure 1. *Weight Distributions*: Box-plot distribution of SIPTWs without deletion and by deletion level for the basic (A) and expanded (B) models

Kilpatrick et al,
PDS, 2013

Inclusion of Highly Weighted Patients has Large Impact on Estimates



Kilpatrick et al, PDS, 20112

Some take-away messages…

- There is an increasing reliance on RWD for decision making concurrent with rapid expansion in data access, methods and audience.
- Consideration of the research question vis a vis what is supported by the real-world data given existing clinical evidence is important.
- Proactive consideration of benefit risk evaluation including by external stakeholders is highly de-risking.
- Industry epidemiologists have an opportunity to further drive the science around elucidation of benefit.