Signal Refinement: Methodological needs

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DoPE BWH

S.S. Potential conflicts of interest

- PI of the Brigham & Women's Hospital DEcIDE Research Center on Comparative Effectiveness Res. (AHRQ)
- PI of the DEcIDE Methods Center (AHRQ)
- Co-investigator of the Mini Sentinel System (FDA)
- No paid consulting or speaker fees from pharmaceutical manufacturers
- Consulting/ board membership in past year:
  - HealthCore; The Lewin Group; RTI; ii4sm; WHISCON
- Investigator-initiated research grants from Pfizer, HealthCore
- Multiple grants from NIH to study all sorts of things

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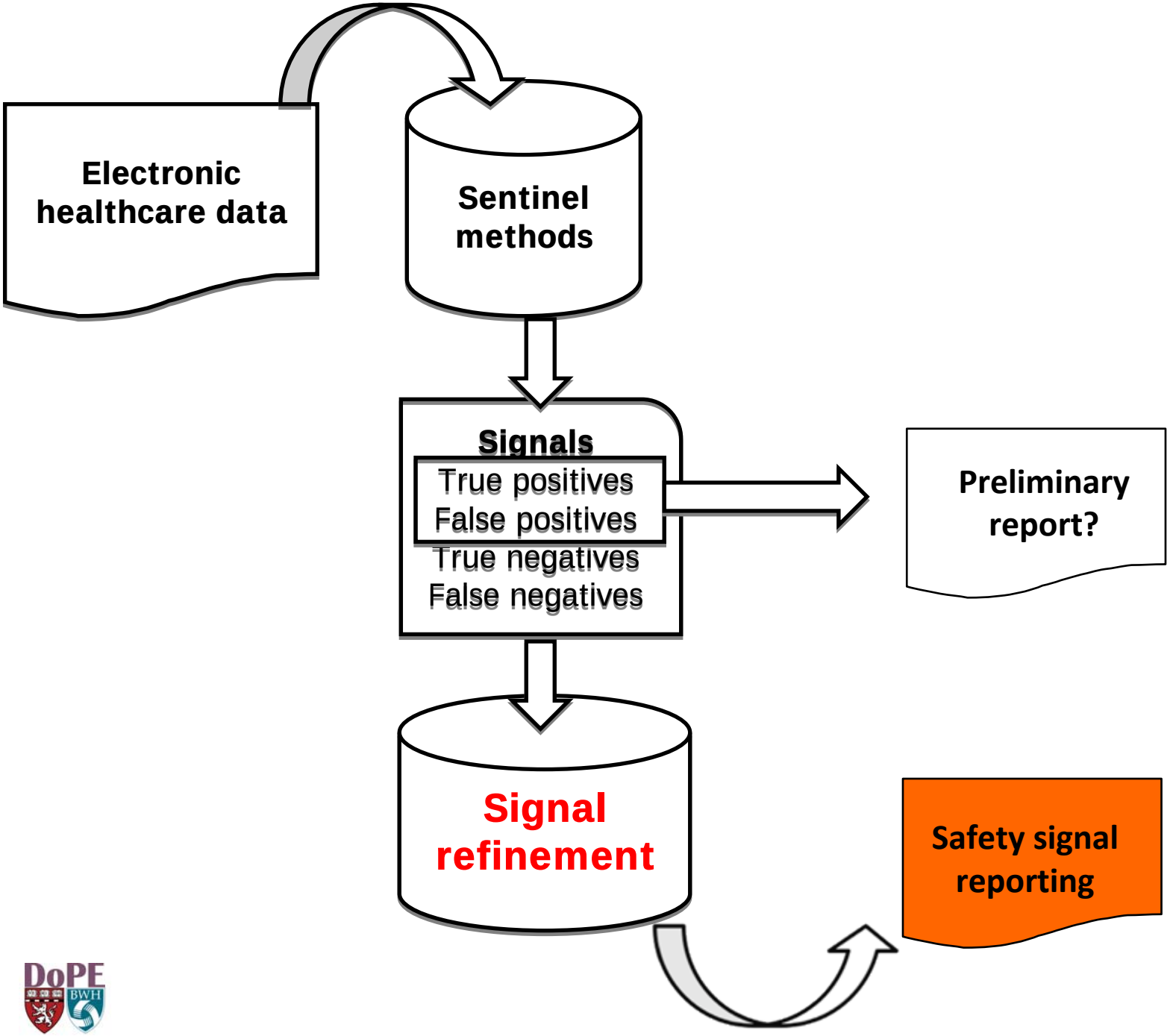
Electronic healthcare data
Sentinel methods
Signals
True positives
False positives
True negatives
False negatives
Preliminary report?
Signal refinement
Safety signal reporting

Setting

- Signals need **rapid** refinement or refutation
  - Ticking time bombs
  - Many signals may be generated -> quickly growing backlog
- Signal refinement needs to be based on solid epidemiologic principles
- Delays in signal refinement may come at a cost to patients

Drug safety surveillance and signal detection

False positive signals:

Causes:

- **Lack of confounder control**
- Differential misclassification
- Multiple testing

Societal cost:

- Withholding a safe and effective drug from some selected patient groups or from all

Statistical Signal generation process:

- Sequential testing
- Relative risk – based analysis
- etc.

False negative signals:

Causes:

- **Lack of confounder control**
- Misclassification of endpoints or exposure
- Insufficient precision

Societal cost:

- Exposing patients to an unnecessary risk
- Marketing with inappropriate risk information

Correct ("true") signals:

Societal gain:

- Removes or restricts unsafe medications quickly
- Makes new risk information available quickly

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What do we want to learn during signal refinement?

- Expand confounder adjustment
- Refine exposure risk window
- Consider dose-response analysis
- Consider duration analysis
- Consider alternative and biologically plausible outcomes
- Consider patient subgroup analyses
- Conduct sensitivity analyses

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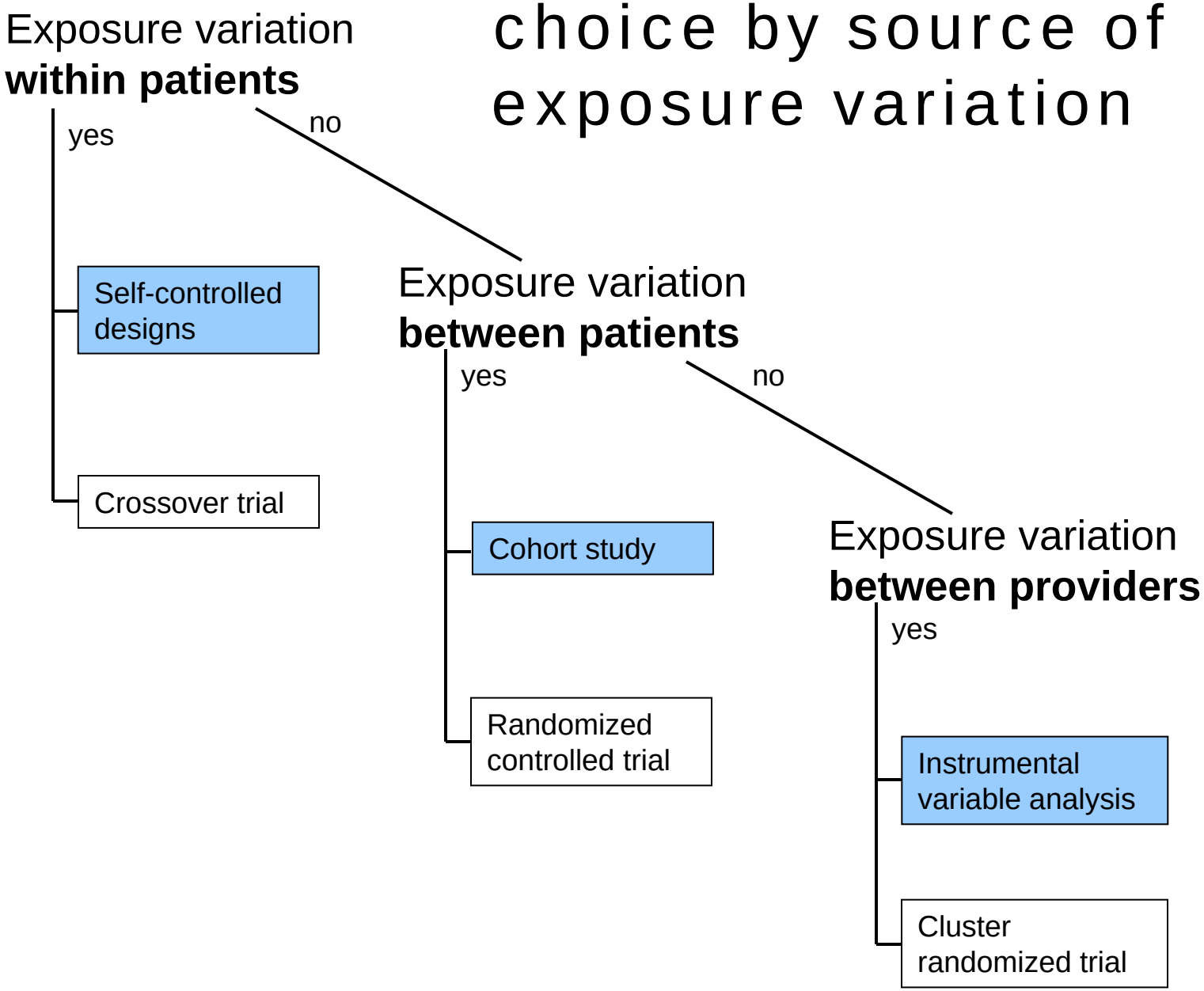
ORIGINAL REPORT

A basic study design for expedited safety signal evaluation based on electronic healthcare data†

- There is no single approach that fits all needs
- However, there are basic guiding principles
- Such principles can serve as framework design that can be adapted to fit the majority of settings
- Framework can be displayed as a flowchart
- Will lead to expedited protocol development
- Will help reduce investigator errors
- Will prepare arguments for justifying design choices

Fundamental design choice by source of exposure variation



Self-controlled designs are preferable

- Controls all time-invariant confounders

But ...

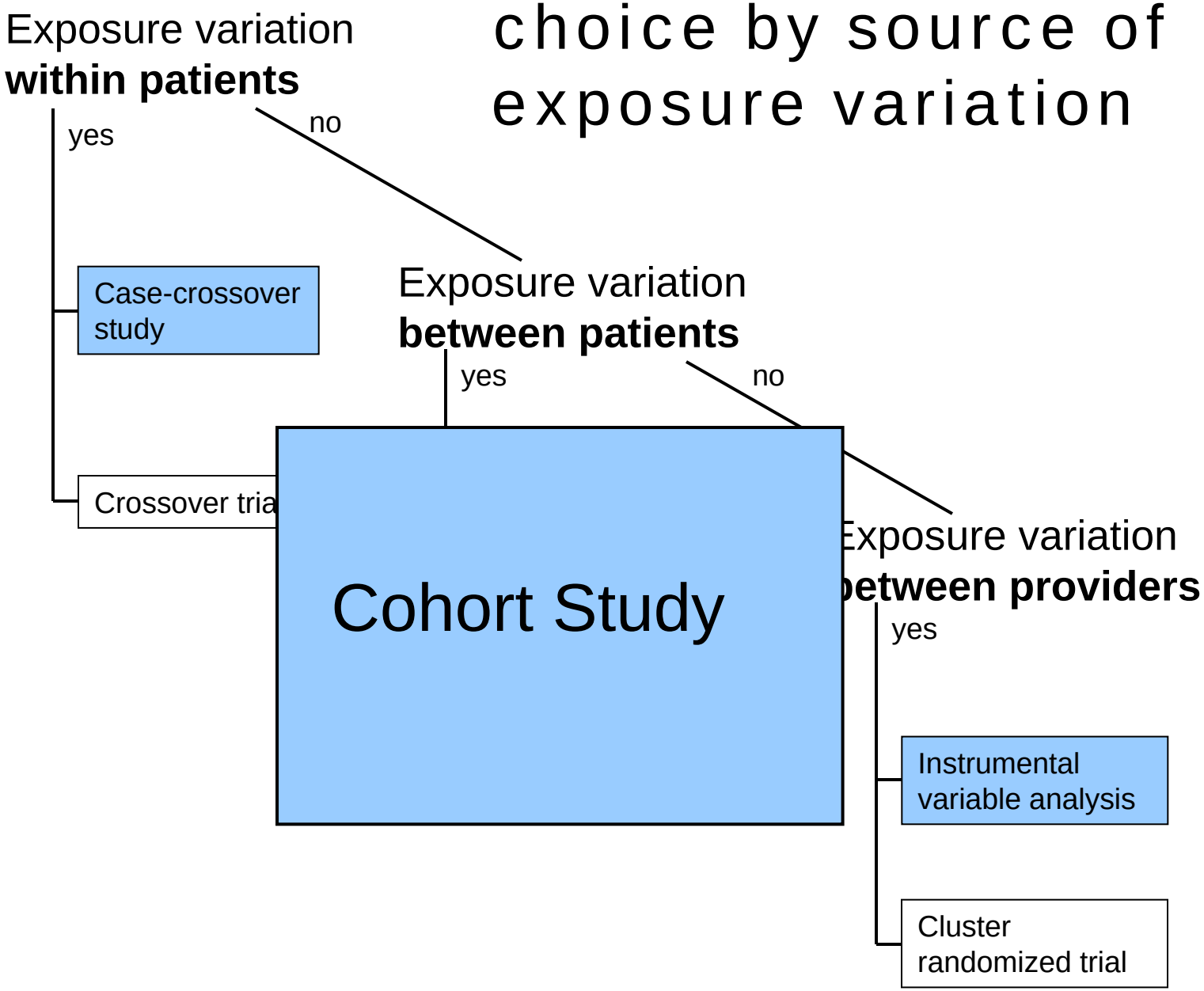
- Requires r
- Requires t
- Requires t
- Is subject
  confoundi
  Decrea
  drug
- Can be ex

iv antibiotics and hepatotoxicity:

- Probably feasible as rapid onset endpoint, transient drug effect

  - However, use of AB might be correlated with symptom-free onset of liver injury or correlated but not causally related with the causes of the injury (think iv antifungals)

Fundamental design choice by source of exposure variation



A cohort-type design

- Incident user design with clear temporality
- Propensity (or disease risk) score adjustment
- Easy to st
- Easy to va
- Dose-resp
- Duration-

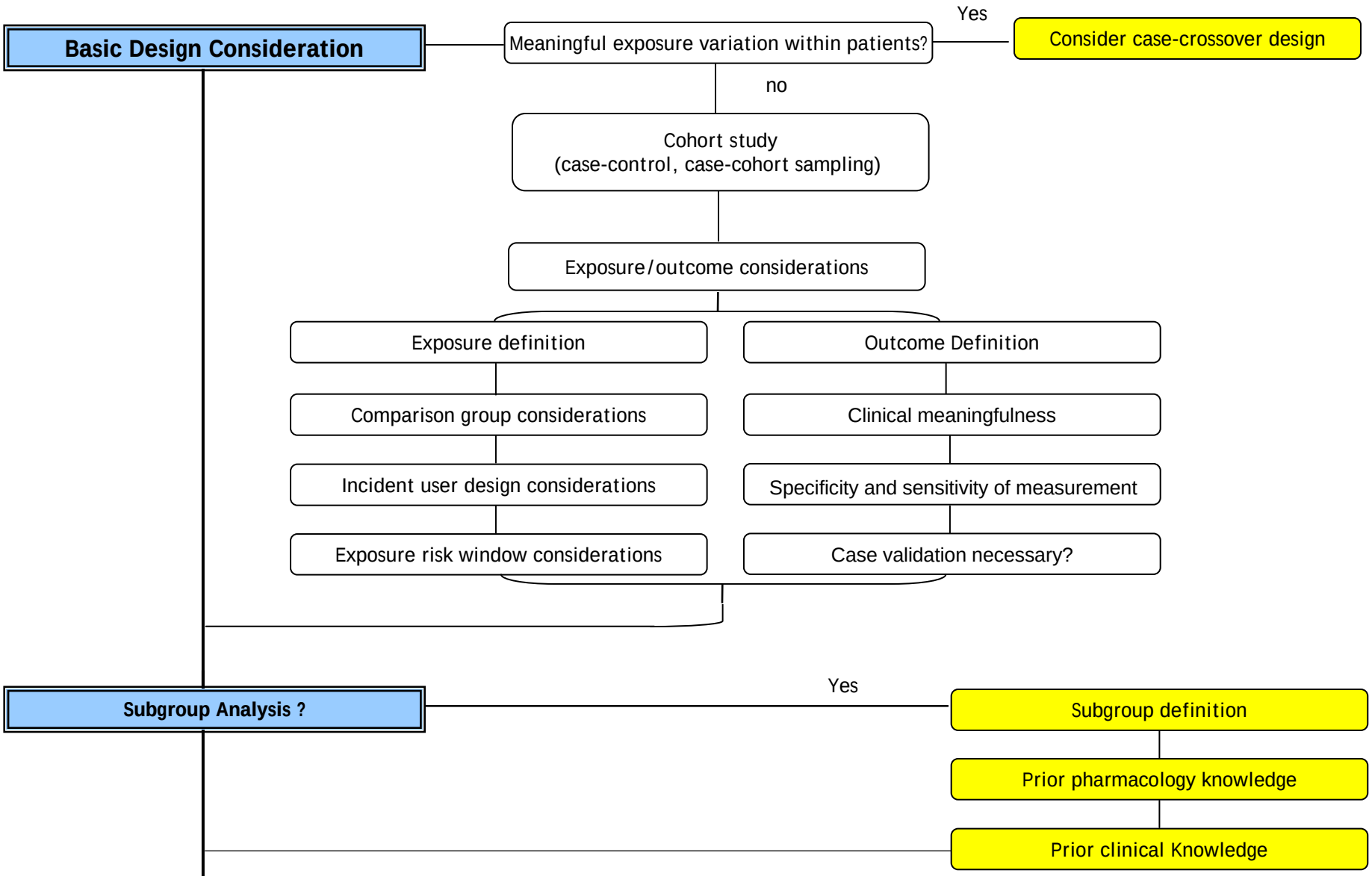
A cohort design is feasible for both
oral AD agent -> MI and
iv AB -> hepatotox.

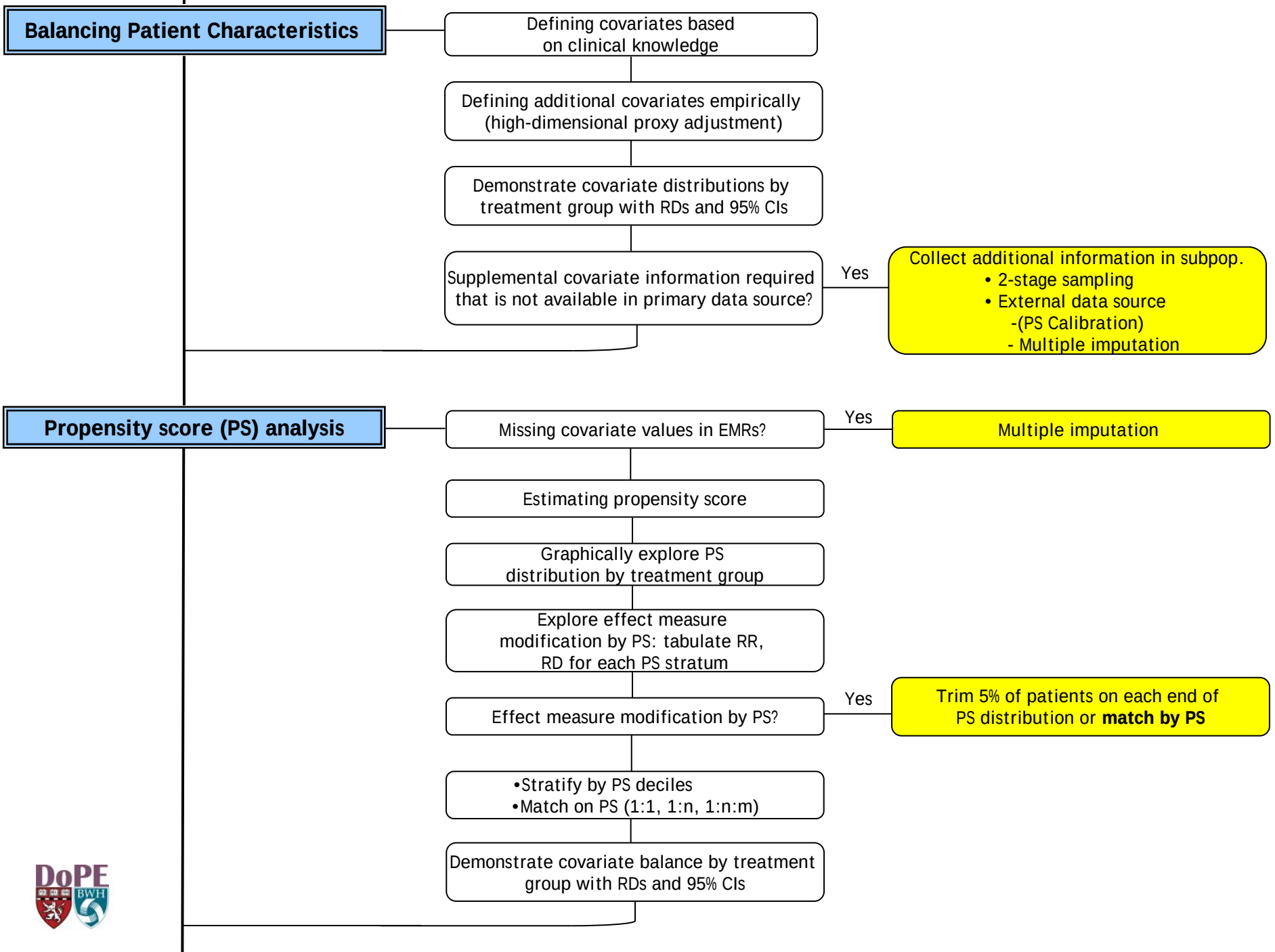
- How challenging is it to find adequate comparison groups?
- How well can confounding be controlled?

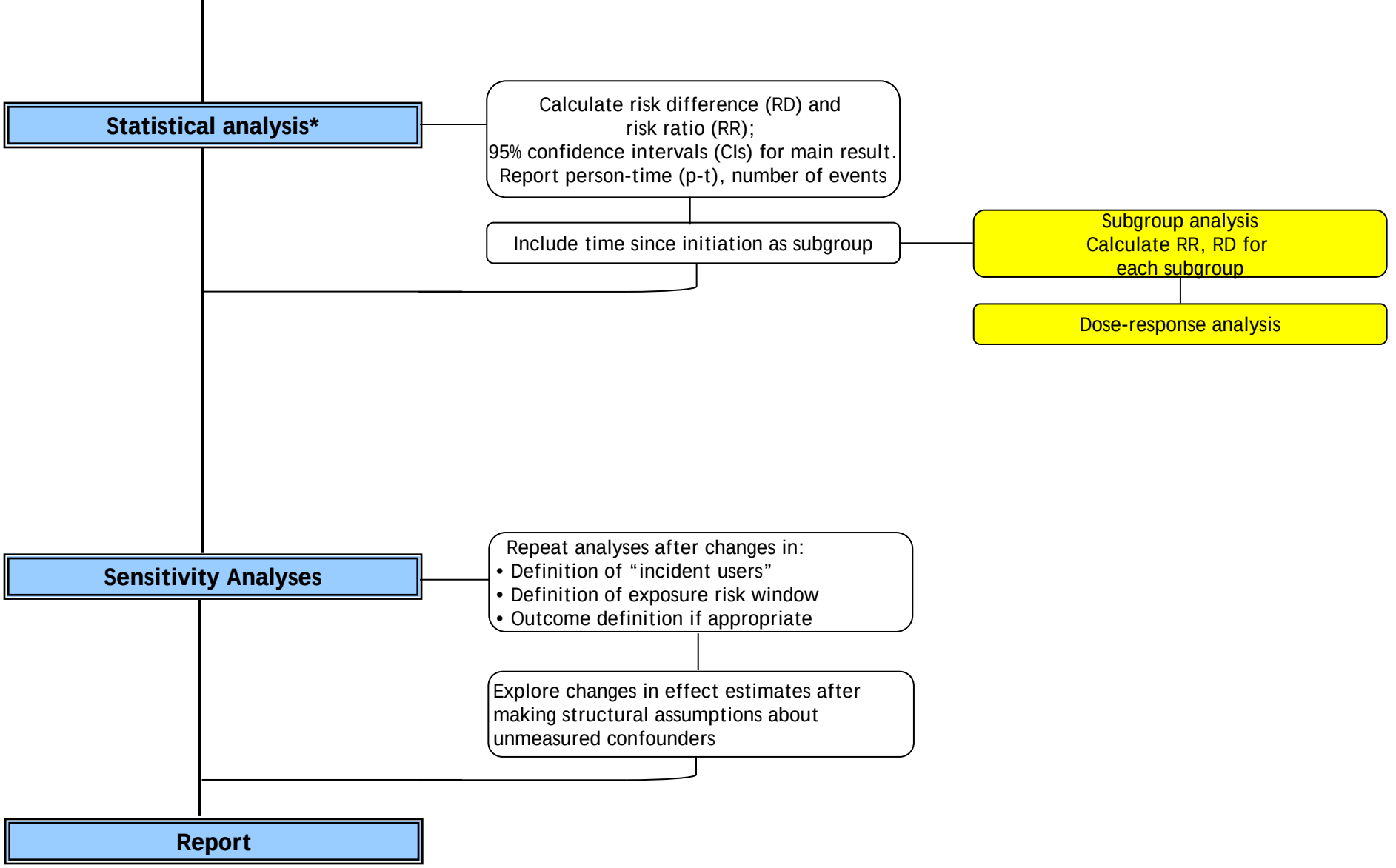
Taxonomy project of Mini Sentinel

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-event link								
			Strength of confounding						
Exposure characteristics *(transient, sustained)*	**Onset of exposure risk window** *(Immediate, delayed)*	**Duration of exposure risk window** *(short, long)*	**Within-person** *(negligible, needs to be addressed)*	**Between-person** *(negligible, needs to be addressed)*	**Event characteristics** *(acute, insidious)*	**Design choice**[b] *(self-controlled, cohort)*	**Background frequency of exposure** *(infrequent, rare)*	**Background frequency of event** *(infrequent, rare)*	**Analytic choice**
Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)	Immediate	Short	Negligible	Negligible	Acute	1 self-controlled (or cohort)	Infrequent	Infrequent	1
								Rare	2
							Rare	Infrequent	3
								Rare	4
					Insidious	2 cohort (or self-controlled)	Infrequent	Infrequent	5
								Rare	6
							Rare	Infrequent	7
								Rare	8
				Needs to be addressed	Acute	3 self-controlled (or cohort)	Infrequent	Infrequent	9
								Rare	10
							Rare	Infrequent	11
								Rare	12
					Insidious	4 self-controlled or cohort	Infrequent	Infrequent	13
								Rare	14
							Rare	Infrequent	15
								Rare	16
			Needs to be addressed	Negligible	Acute	5 cohort	Infrequent	Infrequent	17
								Rare	18
								Infrequent	19


Basic Design Consideration
Meaningful exposure variation within patients?
Yes
Consider case-crossover design
no
Cohort study
(case-control, case-cohort sampling)
Exposure/outcome considerations
Exposure definition
Comparison group considerations
Incident user design considerations
Exposure risk window considerations
Outcome Definition
Clinical meaningfulness
Specificity and sensitivity of measurement
Case validation necessary?
Subgroup Analysis ?
Yes
Subgroup definition
Prior pharmacology knowledge
Prior clinical Knowledge


Balancing Patient Characteristics
Defining covariates based on clinical knowledge
Defining additional covariates empirically (high-dimensional proxy adjustment)
Demonstrate covariate distributions by treatment group with RDs and 95% CIs
Supplemental covariate information required that is not available in primary data source?
Yes
Collect additional information in subpop.
• 2-stage sampling
• External data source
-(PS Calibration)
- Multiple imputation
Propensity score (PS) analysis
Missing covariate values in EMRs?
Yes
Multiple imputation
Estimating propensity score
Graphically explore PS distribution by treatment group
Explore effect measure modification by PS: tabulate RR, RD for each PS stratum
Effect measure modification by PS?
Yes
Trim 5% of patients on each end of PS distribution or match by PS
•Stratify by PS deciles
•Match on PS (1:1, 1:n, 1:n:m)
Demonstrate covariate balance by treatment group with RDs and 95% CIs



*For illustration purposes only an analysis after PS matching is shown.

Methodological needs

- Range of study designs for different types of signals
- Robust methods to adjustment for confounding
- Data that reduce misclassification
- Defining the need for additional detailed patient-level information
- Requirement for rapid protocol development and implementation