Comparative Effectiveness Research of Newly Marketed Drugs

Methodological Challenges

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Potential conflicts of interest

- PI of the Brigham & Women's Hospital DEcIDE-2 Research Center on Comparative Effectiveness Res.
- PI of the DEcIDE Methods Center on Comparative Effectiveness Research (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; WHISCON; Booz & Co
- Investigator-initiated research grants from Pfizer, Novartis, HealthCore
- Multiple grants from NIH to study all sorts of things

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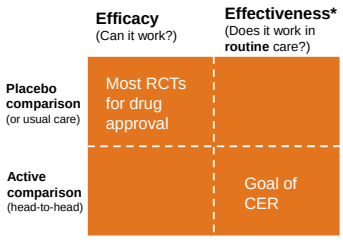
What are the issues arising in CER of newly marketed drugs



- Issues:
  - Non-randomized designs: achieving balance in between trt grps
  - Achieving robust study estimates
  - Dealing with shifts in use patterns over time

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Let's focus first on follow-on medications

- They may have some but limited improvement in effectiveness and/or safety
- Some benefits materialize only in patient subgroups
- They are marketed as such
- As least one if not many alternative drugs are available to treat the labeled indication (e.g. HTN)

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Patient-level issues

- Patients switch from current treatment to new treatment
  - Because of perceived treatment failure
  - Because of perceived adverse outcomes
- As time moves on the patient population receiving the new drug expands and so does the indication
- On-label indication expansion is more often covered by insurance than off-label use

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Physician-level issues

- Early adopters of new technologies
  - Not an analytic problem if this is a random character trait
  - But they may also be those treating sicker patients
  - Or providing better/worse care in general
- Soft on patient demands
  - Triggered by direct-to-consumer marketing

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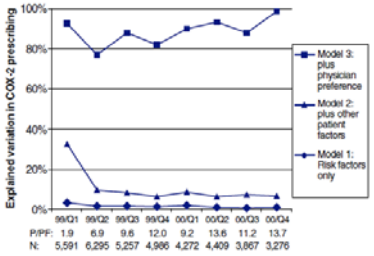
Fig.: Explained variation in treatment choice over time



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System-level issues

- Medication price: out-of-pocket cost
- Formulary positioning (several months lag time)
- Prior authorization (particularly in early months)
- Step-up care requirements
- Treatment guidelines (longer lag time)

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Special issues with first of class medications

- Lack of suitable comparison group
  - Compare to usual care?
  - Is there anybody left who is not treated with new drug?
  - If not, should we use historical controls?
  - Time trend analysis, using time of marketing as IV for an IV analysis?

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Other issues that come to mind

- Lack of statistical power because of few users shortly after marketing
- In a cumulative evidence generation system*, when is enough evidence established?

* Think of FDA's Sentinel System

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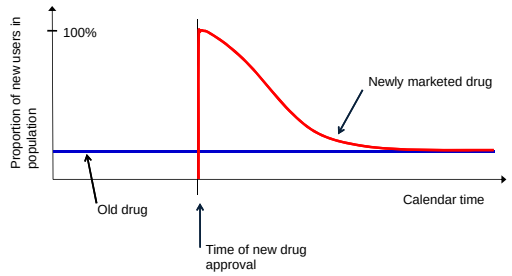
Newly marketed medications



Schneeweiss PDS 2010

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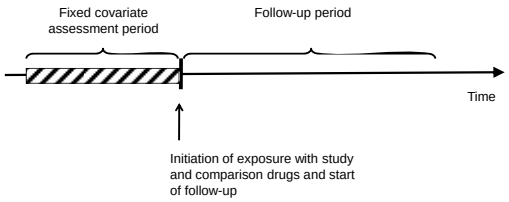
A basic cohort design in longitudinal healthcare claims data



Matching cohorts is different from matching in case-control studies
- e.g. no need for matched analysis

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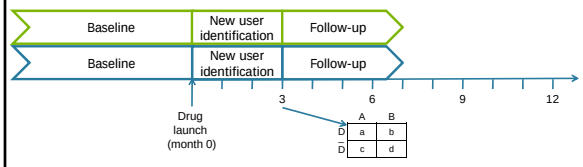
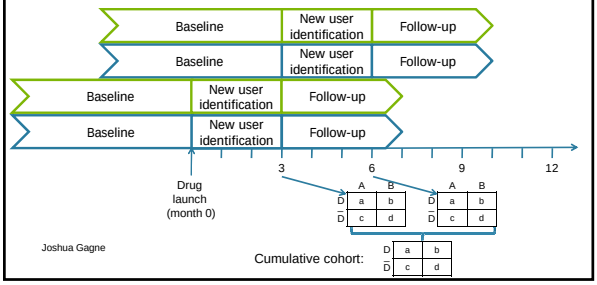
Sequential, PS-matched cohorts



Joshua Gagne

Sequential, PS-matched cohorts



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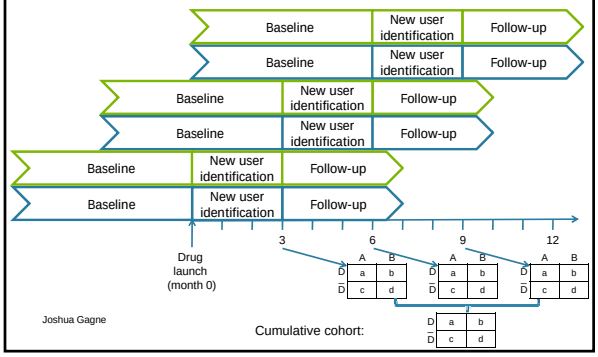

Joshua Gagne

Inspect Table 1 over time

	0 to 6 months		7 to 12 months		13 to 18 months	
	Drug N	Drug O	Drug N	Drug O	Drug N	Drug O
Patient factors	%	%	%	%	%	%
	%	%	%	%	%	%
	%	%	%	%	%	%
	…	…	…	…	…	…
Physician factors	%	%	%	%	%	%
	%	%	%	%	%	%
	%	%	%	%	%	%
	…	…	…	…	…	…
System factors	%	%	%	%	%	%
	%	%	%	%	%	%
	%	%	%	%	%	%
	…	…	…	…	…	…
	M-distance*		M-distance		M-distance	

*Mahalanobis distance

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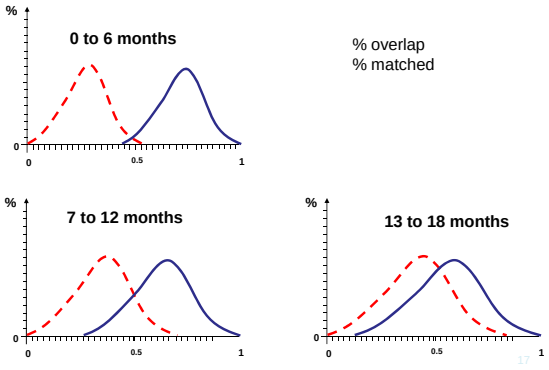
Inspect Propensity score distributions



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On being inpatient

- Wanting to have answers quickly may result in biased results
- Wanting to have answers quickly may result in studies with few and highly selected new users
- With few exposed to the new drug fitting a rich PS model may be difficult -> Disease risk score?
- DRS may be fitted in historical data
  - Less representative for the study population
  - Combination of PS and DRS with time-varying influence on covariate balancing?

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Is there a problem with PS matching?

- Fixed ratio matching: transparency versus efficiency
  - 1:1 or 1:n matching produces nice Table 1's
  - 1:n matching will lead to discarding some potential matches
- Multiple reference groups: new high-dimensional optimal matching algorithm now available
- With few exposed to the new drug fitting a rich PS model may be difficult -> Disease risk score?
- DRS may be fitted in historical data
  - Less representative for the study population
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Thank you very much

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How to demonstrate changes in treatment choice confounding over time

- Table 1 comparisons
- Malhalanobis distance
- Explained variation and components of variation (R2, c)
- Propensity score distributions (% overlap, % matched)

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