Challenges of Generating the Required Evidence: An Industry (Scientist's) Perspective

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Disclosure

- Full-time employee of Janssen Research & Development
- Shareholder of Johnson & Johnson Stock
- Represent my views and not necessarily those of my company or other companies.

Goal from a Pharma Perspective

Generate credible evidence of value in real world use that will inform as many decisions as possible.

Options include

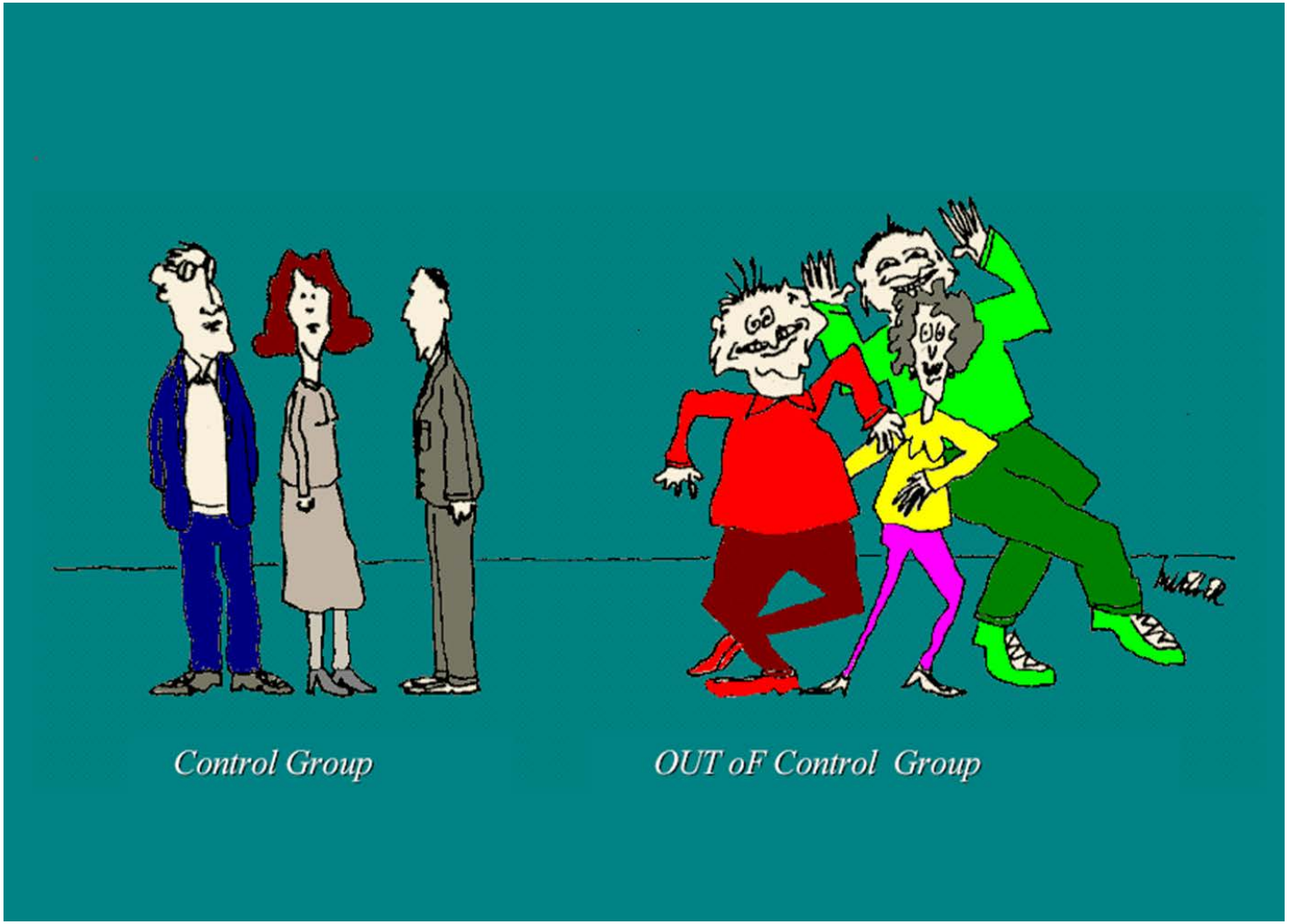
- **Observational database studies or Registries**: potential issues with bias/confounding; adequate sample size (due to market penetration)

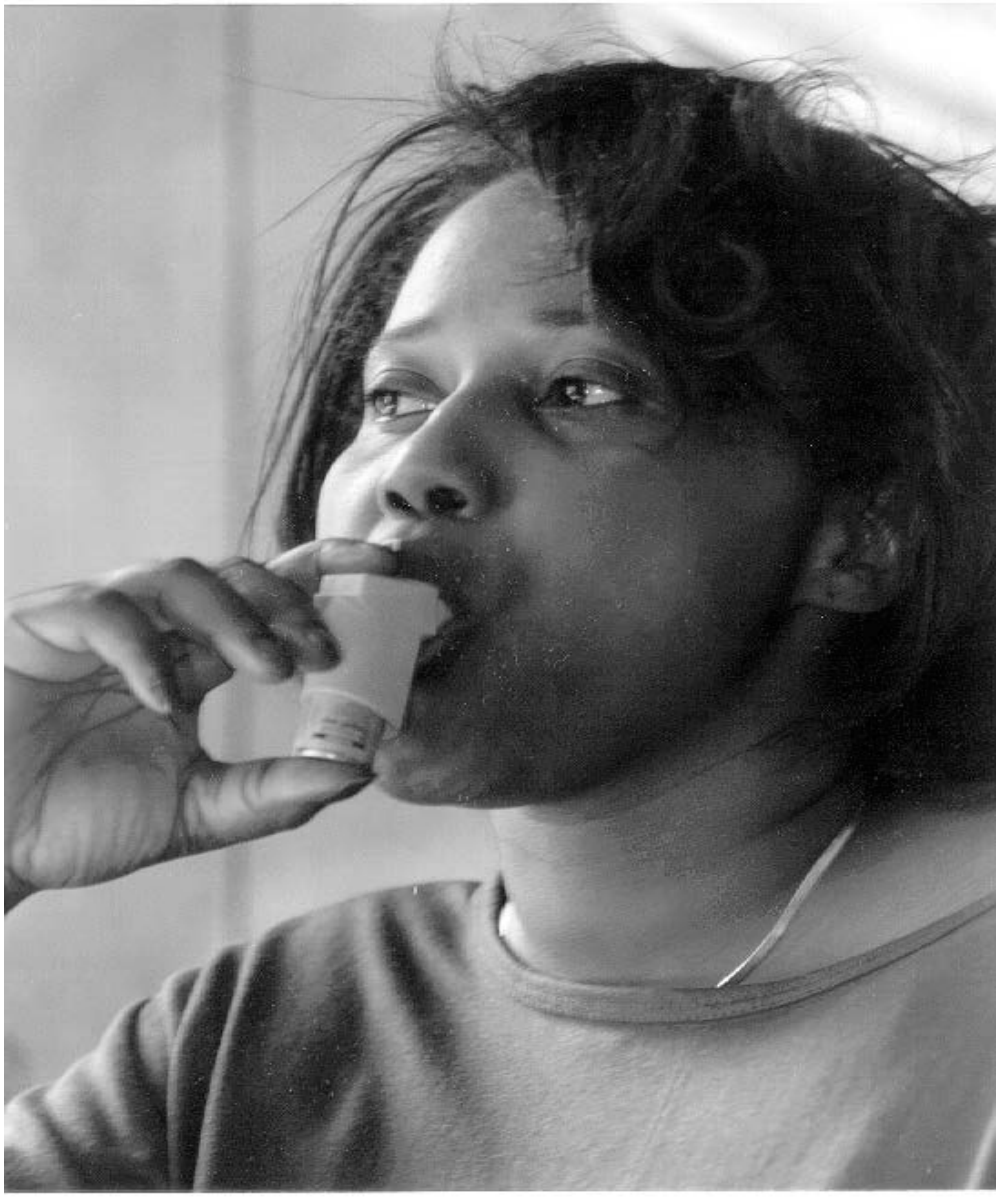
- **Randomized trials in more 'real world' populations/settings**: Pragmatic trials, randomizing into the database

Key Decisions to Align

- **Comparator** (may vary across payers)
- **Relevant population**: Payer's own ?
  - Adequate infrastructure and patient numbers
  - Multiple payers with different benefit designs and populations---do you need multiple trials?
- **Use of surrogates and 'value' of longer term outcomes**
- 'Value' and impact of
  - Assuring appropriate on-label use and dose
  - Indirect costs/patient viewpoint: Productivity, QoL
- What constitutes a **'meaningful' difference** in value/effectiveness?

THE REAL WORLD IS A VERY NOISY PLACE…..





The News and Observer Sunday, December 8, 1991

"An inhaler prescribed by her doctor helps Gail Pouncy's smoke-scarred lungs- like many survivors, she suffered respiratory injuries in the Imperial fire."

We do use our observational databases to examine the differences between the RCT population and the real-world population of users

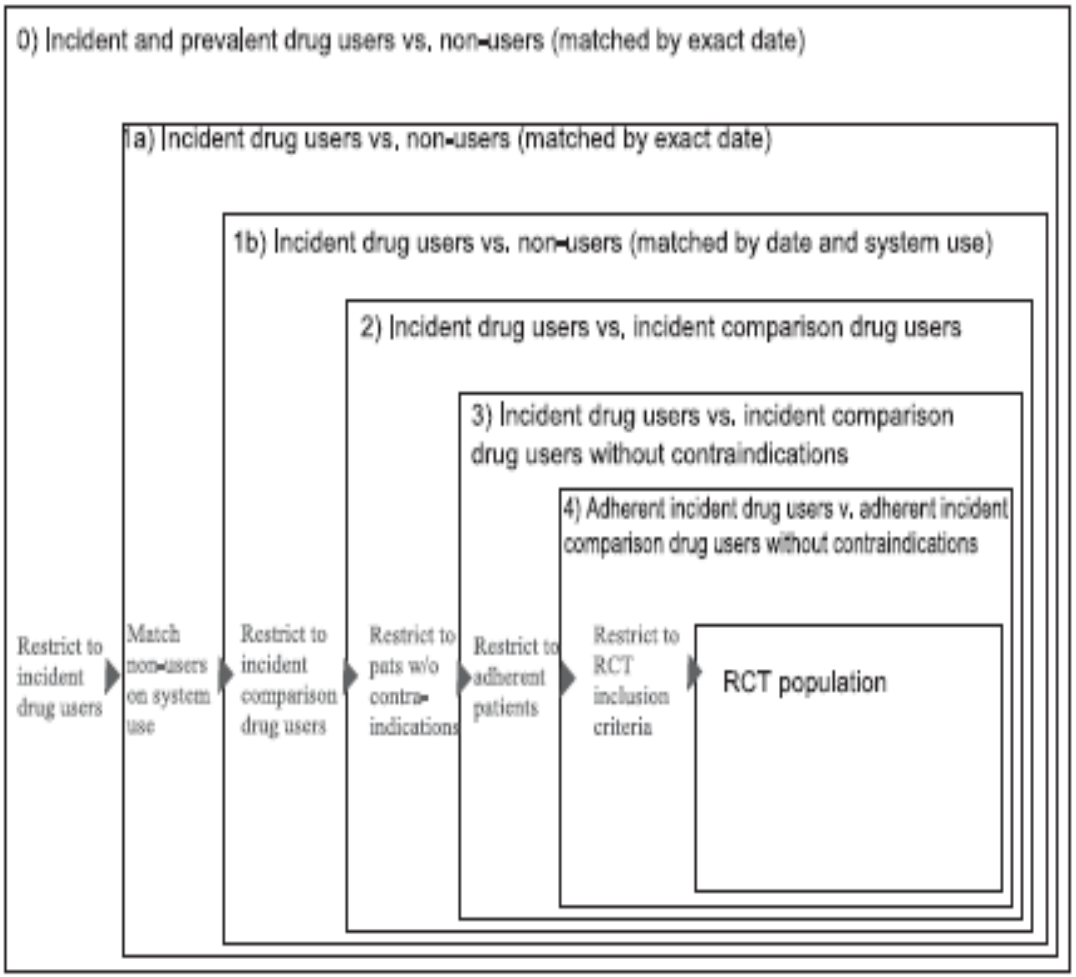


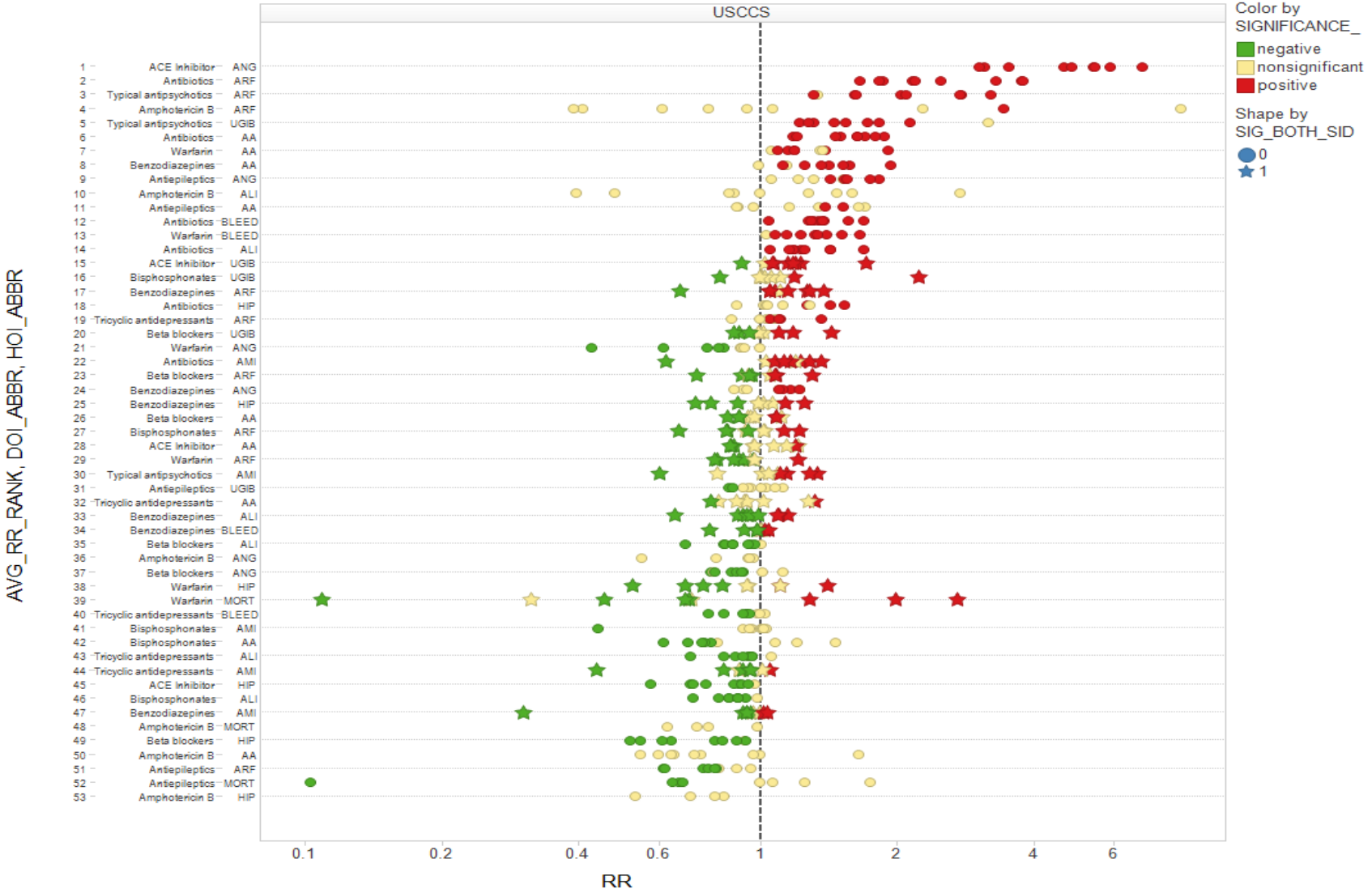
FIGURE 1. Five consecutive population restrictions to approximate RCTs in pharmacoepidemiologic database studies.

Schneeweiss et al.: Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results. *Med Care* 2007; 45: S131–S142.

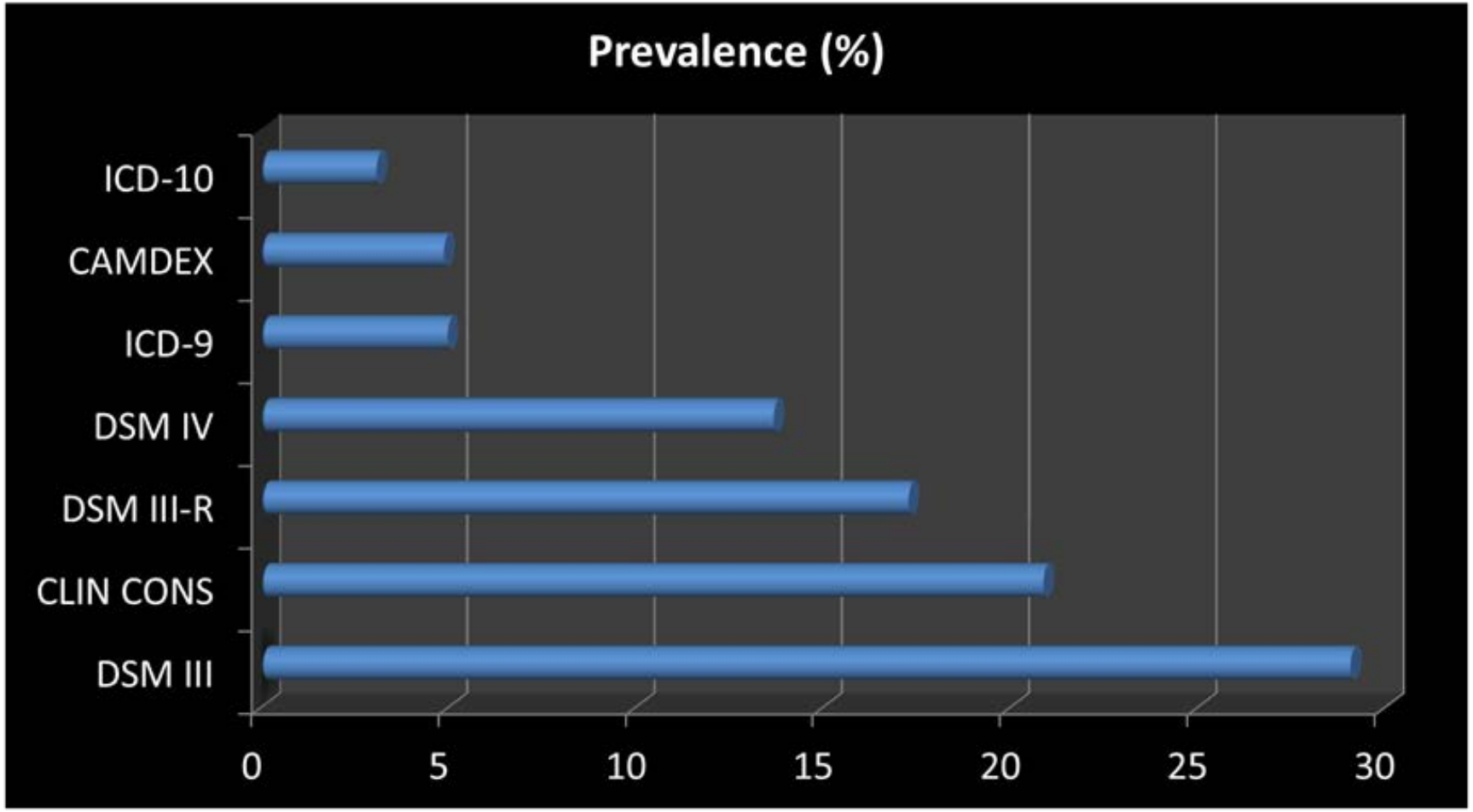
POPULATIONS DIFFER:
Heterogeneity due to data source in OMOP

(self-controlled case series)

(from OMOP presentations http://omop.org/2013Symposium)



Which definition for Dementia?



Created from Erkinjuntti T, Masbye T, Steenhuis R, Hachinski V: The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med 337:1667-1774, 1997

What will be the impact of another study?
NSAIDS and Prevention of Dementia
Observational Data + / RCT data -

Study reference	Overall cohort	Duration NSAID use	AD cases	Risk ratio	95% confidence interval
PROSPECTIVE STUDIES					
Stewart et al. (1997)	1,686	≥2 years	81	0.40	0.19–0.84
		<2 years		0.65	0.33–1.29
in't Veld et al. (2001)	6,989	≥2 years	4	0.20	0.05–0.83
		1–23 months	210	0.83	0.62–1.11
		<1 month	88	0.95	0.70–1.29
Breteler et al. (2002)	7,983	≥18 months	293	0.60	0.30–1.20
Zandi et al. (2002)	3,224	≥2 years	104	0.45	0.17–0.79
Cornelius et al. (2004)	1,301	NA	164	0.61	0.32–1.15
Haag et al. (2006)	6,992	≥2 years	582	0.65	0.40–1.06
Szekely et al. (2008a)	3,229	NA	321	0.63	0.45–0.88
Arvanitakis et al. (2008)	1,019	NA	209	1.19	0.87–1.62
Breitner et al. (2009)	2,736	NA	356	1.57	1.10–2.23
RETROSPECTIVE STUDIES					
Landi et al. (2003)	2,708	NA	269	0.43	0.23–0.82
Yip et al. (2005)	1,034	>6 months	61	0.64	0.24–0.98
Vlad et al. (2008)	246,199	>5 years	49,349	0.76	0.68–0.85
		>4 to ≤5 years		0.76	0.69–0.84
		>3 to ≤4 years		0.90	0.84–0.97
		>2 to ≤3 years		0.93	0.88–0.99
		>1 to ≤2 years		0.90	0.86–0.94
		≤1 year		0.98	0.95–1.00

NA: not applicable.

Front. Aging Neurosci., 21 May 2010 | http://dx.doi.org/10.3389/fnagi.2010.00019

We are finding that well-designed observational studies approximate the effects of treatment as well as randomized controlled trials on the same topic.

Concato et al: NEJM 2000; 342: 1887-1892; Benson and Hartz: NEJM 2000; 342:1878-1886.

Our results provide little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, inclusion of pharmacological studies, or use of propensity score adjustment. Anglemyer A, Horvath HT, Bero L: Cochrane Database of Systematic Reviews 2014, Issue 4.

Decision Making for the Company

- **Cost**: Trials can be much larger, take longer, and more expensive than many realize
  - Noisiness in the real world affects sample size/power
  - Experience of practices that will participate in research
  - Efficient designs: hybrid, use of EHR
- **Incremental impact** of the study on decision given existing body of RCTs and observational studies
- **Applicability/generalizability** of findings with other payers
- **Trade-off on Type I error: Internal validity vs. generalizability**
- **Penetration of product** / availability of relevant subjects (both for retrospective and prospective)
- Population mean vs. individual effects