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MEDICINE

# STRengthening Analytical Thinking for Observational Studies: STRATOS initiative: **Study Design**

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# Acknowledgments & Conflicts of Interest

European Commission appointed independent Member of Pharmacovigilance & Risk Assessment Committee of EU at the European Medicines Agency

Member of CIOMS Working Group on Meta-analysis for safety LSHTM (but not SE) funded by several pharmaceutical companies

Member of expert working groups at the UK Medicines & Healthcare Products Regulatory Agency (MHRA)

*All remarks are a personal viewpoint and have not been approved by other members of TG5*



# STRATOS

- STROBE has provided guidance on *Reporting*
- STRATOS is an attempt to improve conduct
  - ENCePP has guidance on methods-[http://www.encepp.eu/standards\\_and\\_guidances/documents/ENCePPGuideofMethStandardsinPE\\_Rev4.pdf](http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev4.pdf)
- Guidance on reporting is like lighting up a room-not saying if it is clean
- Critical appraisal is saying if it is clean enough-
  - Operating theatre or coal shed?
- Guidance on conduct is to make sure the room is clean enough



**Communication**

**Report Writing**

**Analysis**

**Execution**

**Planning**

**Design**

**Objectives**



# Some principles

- single observational studies rarely definitive (or perfect!)
- Assessing epidemiologic evidence -> a process of triangulation across studies, aim to contribute to the pool of knowledge
- different populations, variety of designs, investigators, and methods,
- often involving meta-analysis (not “top of the hierarchy”) & integration of data from variety of sources and study types
- obtain valid effect estimates in a particular population during a particular risk period



# Purposes

## 1. Descriptive

- Disease oriented
- Intervention oriented
  - Intervention utilisation
    - E.g. Compliance with Summary of Product Characteristics (label)
  - Risk factor distribution
  - Spontaneous reports of adverse drug reactions

## 2. Comparative

- Causal effects; benefits, comparative effectiveness, harms

# Comparative studies

## The main focus of epidemiology



- They will usually want to estimate causal effects; {Safety- demonstrated absence of harm}
  - Usually they focus on harms, but may also look at-
    - Benefits (often reduction in harm), comparative effectiveness,
  - Moves towards formal decision making for risk/benefit
    - Will require confirmation of benefit from RCTs in practice



# Main Comparative designs

- Randomised Controlled Trials (RCTs)
  - Systematic reviews (SRs) of RCTs
- Cohort Studies
  - “Field” studies; registry-based; databases
- Case-control studies
  - “Field” studies; registry-based/aided; databases
- Distinguish incidence and prevalence in each



# Time has only one direction

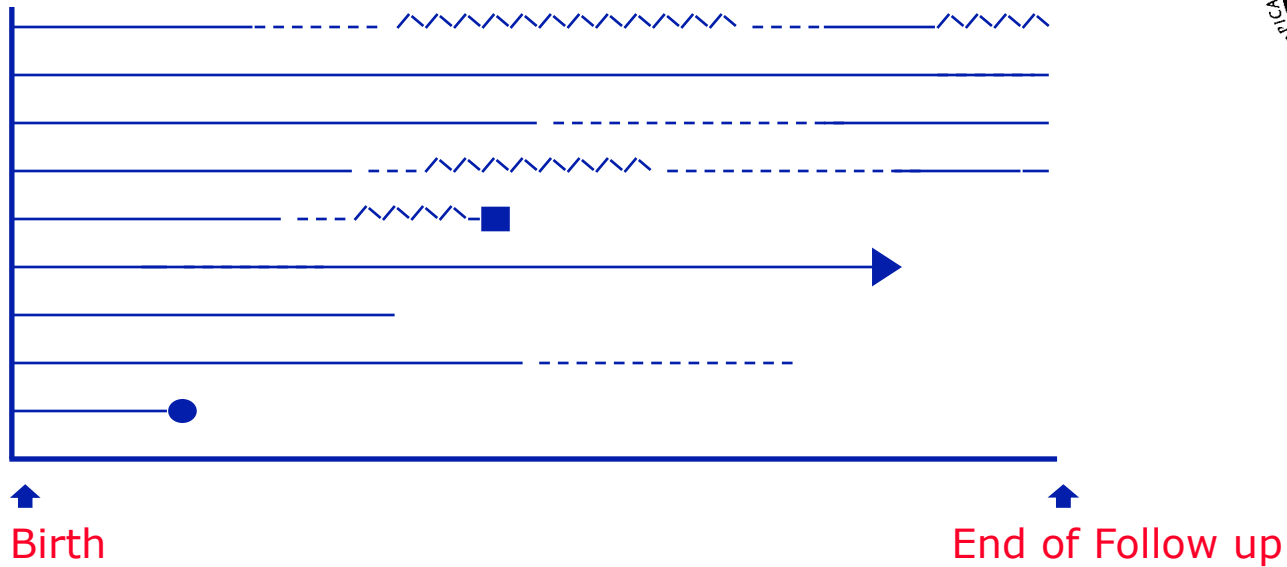


- In some senses all studies are based on a cohort
- RCTs have random allocation to treatment, then follow-up
- Observational studies have non-random allocation and **follow-up** (though if totally deterministic, then extra information outside study or strong, untestable, assumptions required to interpret them)
- The issues are
  - what is the source population?
  - what is the outcome?
    - (Incidence or prevalence)
  - How is the sampling done?



# Study Design Options

- All epidemiological studies are (or should be) based on a particular population (the **source population**) followed over a particular period of time (the **risk period**)
- The different study design options differ only in how the source population is defined and how information is drawn from this population and time period



- Death
- ▶ other death
- lost to follow up
- “non-diseased”
- - - symptoms
- ^^ severe disease



# Cohort studies

- define a source population - exposed & unexposed
  - follow-up (FU) to event
- Not just in databases or even in large longitudinal cohort studies (ALSPAC, National Cohorts, 1958, 1970)
  - Some cohort studies (often registry-based) have no valid comparative groups)
- `Self-Controlled Case Series' is a special case
- Case-cohort design {sample <100% non-cases}



# Incidence and Prevalence

- ***Incidence*** is the number of new cases of the condition over a specified period of time
- ***Prevalence*** is the number of cases of the condition at a particular point in time

# A Hypothetical Incidence Study

	<b>Exposed</b>	<b>Non-exposed</b>	<b>Ratio</b>
<b>Cases</b>	<b>1,813</b>	<b>952</b>	
<b>Non-cases</b>	<b>8,187</b>	<b>9,048</b>	
<b>Total</b>	<b>10,000</b>	<b>10,000</b>	
<b>Person-years</b>	<b>90,635</b>	<b>95,163</b>	
<b>Incidence rate</b>	<b>0.0200</b>	<b>0.0100</b>	<b>2.00</b>
<b>Incidence proportion (risk)</b>	<b>0.1813</b>	<b>0.0952</b>	<b>1.90</b>
<b>Incidence odds</b>	<b>0.2214</b>	<b>0.1052</b>	<b>2.11</b>

# A Hypothetical Case-Control Study

	Exposed	Non-exposed	Odds
Cases	1,813	952	1,813/952
Controls	1,313	1,452	1,313/1,452
Odds	1,813/1,313	952/1,452	
Odds ratio			2.11



# Odds Ratio

- $OR = (1813/1313) / (952/1452) = 2.11$
- This *incidence case-control study* yields the same estimate as would have been obtained by an incidence study but with a much smaller number of participants because we include *all* of the cases but only a *sample* of the non-cases





# Methods of Sampling Controls

- From *survivors* (non-cases at end of follow-up) = cumulative sampling
- From *source population* = case-cohort sampling
- From *person-years* = density sampling

# Methods of Sampling Controls

	Exposed	Non-exposed	Odds ratio
<b>Cases</b>	<b>1,813</b>	<b>952</b>	
<b>Controls</b>			
from survivors	<b>1,313</b>	<b>1,452</b>	<b>2.11</b>
from source population	<b>1,383</b>	<b>1,383</b>	<b>1.90</b>
from person-year	<b>1,349</b>	<b>1,416</b>	<b>2.00</b>



# Misconceptions re: Case-Control Studies

- Proceeds from effect (disease) to cause (exposure), i.e. reverse causality
- Inherently more prone to bias than cohort studies
- Odds ratio only approximately estimates the relative risk
- Depends on a “rare disease” assumption
- book by Keogh & Cox for modern views (Cambridge UP 2014)

# Prevalence Case-Control Studies



This *prevalence case-control study* yields the same estimate as would have been obtained by a prevalence study but with a much smaller number of participants because we include *all* of the prevalent cases but only a *sample* of the non-cases



# Study Design Options

**Sampling on  
outcome**

**No**

**Yes**

**Study  
outcome**

**Incidence**

**Incidence  
studies**

**Incidence  
case-control  
studies**

**Prevalence**

**Prevalence  
studies**

**Prevalence  
case-control  
studies**



# Strengths & weaknesses - RCTs

- RCTs strong for causal inference (but not perfect)
  - confounders not usually relevant {but see Williamson et al Stat Med. 2014; 33(5): 721–737}
  - Might be done in registries or databases
  - Staa TP et al. Pragmatic randomised trials using routine electronic health records: putting them to the test. BMJ. 2012;344:e55. also Pharmacoepidemiology session
  - New NEJM paper: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1308789>
- Weaknesses
  - Many biases can arise – selective publication worst for pepi
  - Costly in time & resources; unrepresentative?
  - Short FU; small sample size for clinical harms (& benefits?)
  - Elderly, pregnant, co-morbidity & co-prescription limited

# Observational Medical Outcomes Partnership Third Annual Symposium

A Public Private Partnership of  
THE FOUNDATION  
FOR THE NATIONAL  
INSTITUTES OF HEALTH

June 28, 2012 | Bethesda North Marriott Hotel & Conference Center | Bethesda, Maryland | <http://omop.fnih.org>

## **These slides are a selection from the OMOP symposium in June 2012**

Used with permission

Thanks to Paul Stang & Patrick Ryan

See also special issue of *Drug Safety* 2013;36 Suppl 1:S3-4.

# Ground truth for OMOP 2011/2012 experiments

	Positive controls	Negative controls	Total
<b>Acute Liver Injury</b>	81	37	118
<b>Acute Myocardial Infarction</b>	36	66	102
<b>Acute Renal Failure</b>	24	64	88
<b>Upper Gastrointestinal Bleeding</b>	24	67	91
<b>Total</b>	165	234	399

isoniazid

fluticasone

indomethacin

clindamycin

ibuprofen

loratadine

sertraline

pioglitazone

Criteria for positive controls:

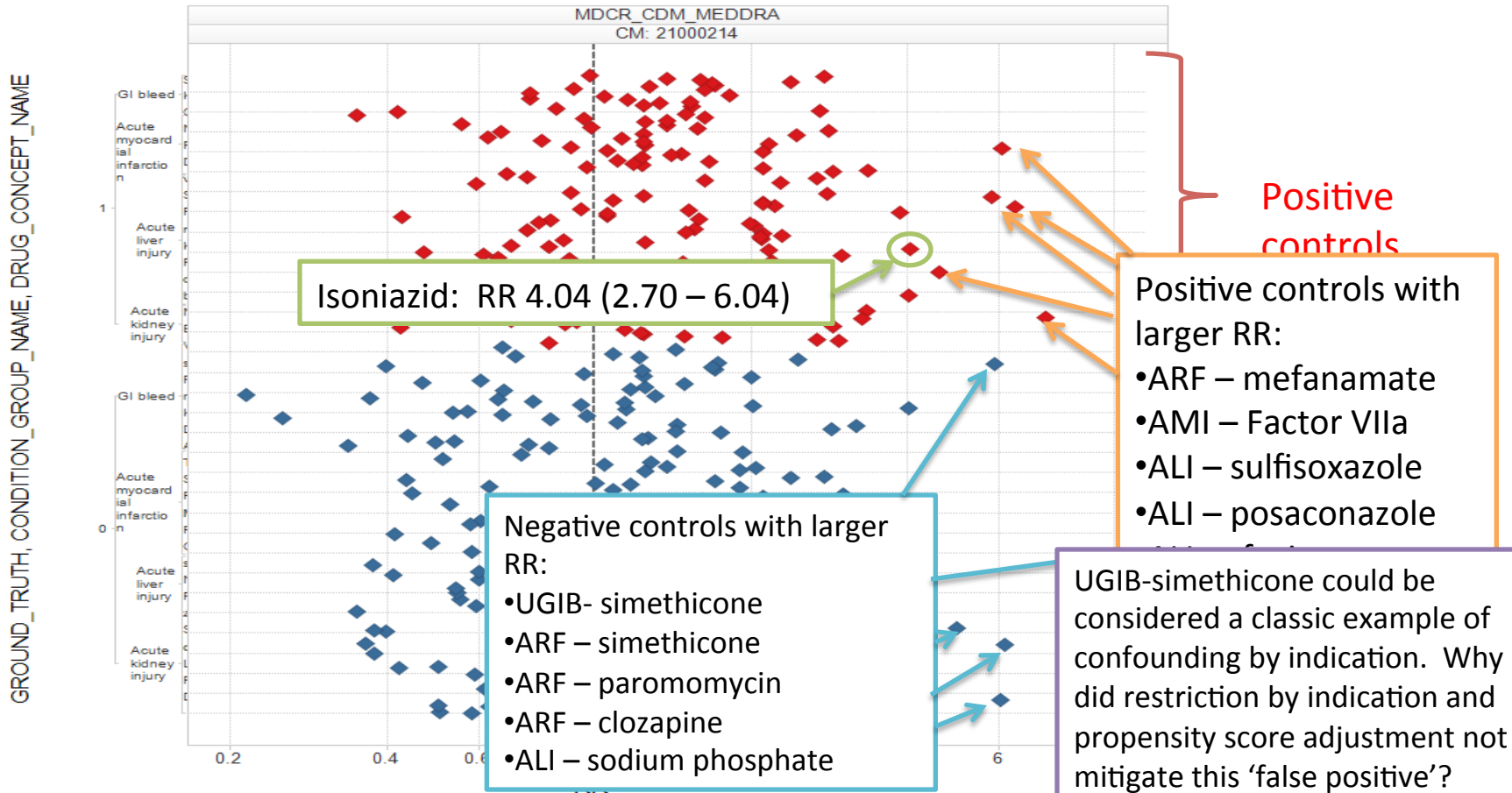
- Event listed in Boxed Warning or Warnings/Precautions section of active FDA structured product label
- Drug listed as 'causative agent' in Tisdale et al. 2010: "Drug-Induced Diseases"

Criteria for negative controls:

- Event not listed anywhere in any section of active FDA structured product label
- Drug not listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Literature review identified no powered studies with evidence of potential positive association



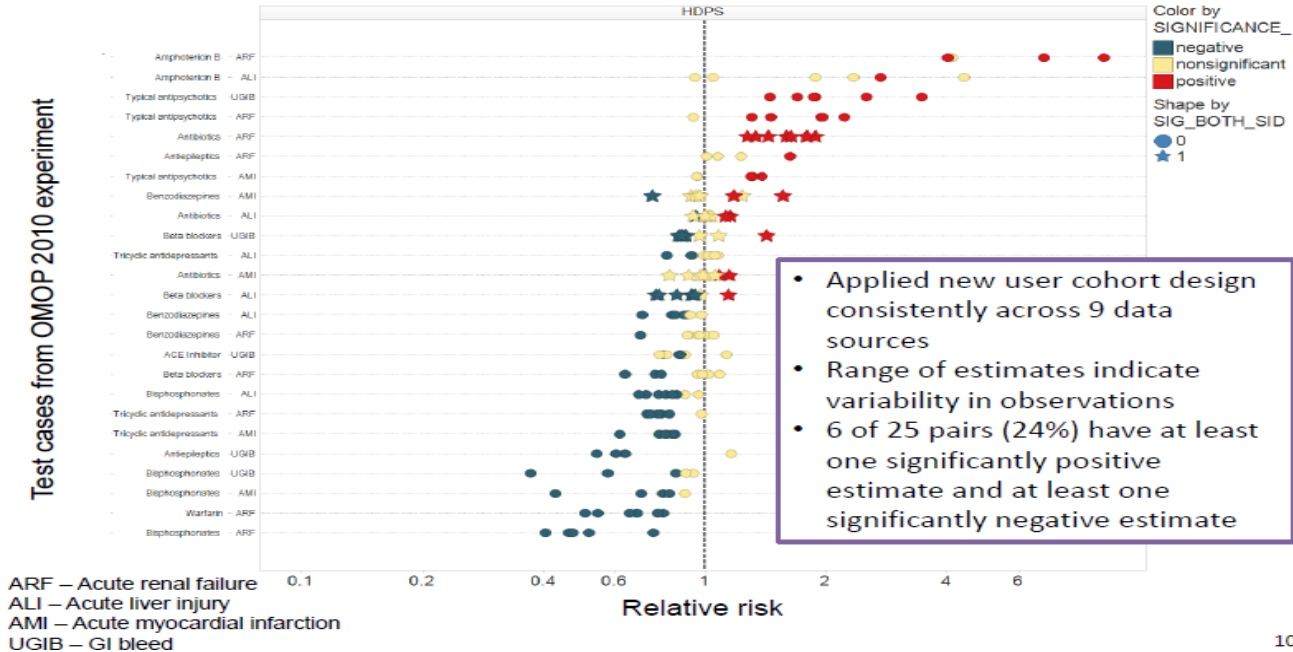
# New user cohort design applied to all test cases



# New user cohort from OMOP (*Drug Safety 2013*)

OBSERVATIONAL  
MEDICAL  
OUTCOMES  
PARTNERSHIP

## Heterogeneity due to data source



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# Protocols

- Must have research question and objectives
- Should be registered e.g-  
<http://www.encepp.eu/encepp/studiesDatabase.jsp>
  - Declaration of Helsinki requires registration
- Design specified in detail in protocol
- Statistical analysis plan should be included



# Aspects of Design for comparison

- Structure
  - Baker MA et al. A vaccine study design selection framework ...*rapid.. monitoring. Am J Epidemiol.* 2015;181:608-18
- Designs described- case-control , self-controlled risk interval, self-controlled case series method, case-crossover
- All used for vaccine safety surveillance
- Exploratory designs (& analysis) should be clearly described as exploratory



# Selection criteria

- Perrio et al (2007) *Pharmacoepidem. Drug Safe.*, 16: 329–336.
- Showed exclusion criteria widely used in pharmacoepidemiology but not well studied.
  - Exclusion criteria relating to data quality and validation were the most commonly applied (87% of publications), followed by patient characteristics (75%), disease-related (69%), exposure-related (38%) and miscellaneous (3%)



# Is there a crisis in epidemiology?

- Stan Young “Any claim coming from an observational study is most likely to be wrong.” Young, S. S. and Karr, A. (2011), Deming, data and observational studies. *Significance*, 8: 116–120.
- John Ioannidis- 2015. Video of lecture can be watched through this website-. [www.lshtm.ac.uk/newsevents/events/2015/07/24th-bradford-hill-memorial-lecture](http://www.lshtm.ac.uk/newsevents/events/2015/07/24th-bradford-hill-memorial-lecture)
- Replication of studies is not done often enough
  - Open data less likely in epidemiology
    - Alsheikh-Ali AA et al. Public availability of published research data in high-impact journals. PLoS ONE 6, e24357 (2011).



# STRATOS

- The challenge is to bring statistical *thinking* into observational research including design
- We cannot write a textbook on observational research
- We may have to look at where investigators go wrong but show how we can do it well