# Research Methodology in Pharmacoepidemiology

**Dr. Kwame Appenteng**
**5th MURIA Workshop/Symposium**
**July 2019**

## Acknowledgement

Stephen Motsko, PharmD, PhD

Nicole Kellier, PhD

## Outline

- Epidemiologic study designs
- Definition of exposure and outcome in PE studies
- Meta-Analyses
- Sample size calculations

## Epidemiologic study designs

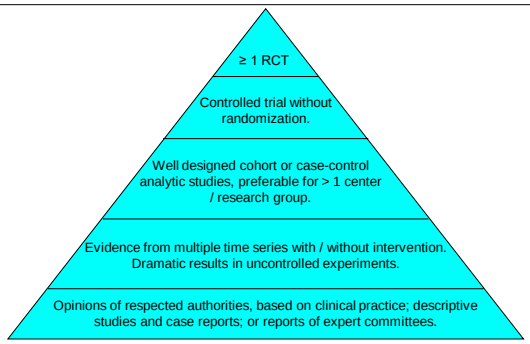
Table 2.4. Advantages and disadvantages of epidemiologic study designs

| Study Design | Advantages | Disadvantages |
|---|---|---|
| Randomized clinical trial (Experimental study) | Most convincing design<br>Only design which controls for unknown or unmeasurable confounders | Most expensive<br>Artificial. Logistically most difficult. Ethical objections |
| Cohort study | Can study multiple outcomes<br>Can study uncommon exposures<br>Selection bias less likely<br>Unbiased exposure data<br>Incidence data available | Possibly biased outcome data<br>More expensive<br>If done prospectively, may take years to complete |
| Case–control study | Can study multiple exposures<br>Can study uncommon diseases<br>Logistically easier and faster<br>Less expensive | Control selection problematic<br>Possibly biased exposure data |
| Analyses of secular trends | Can provide rapid answers | No control of confounding |
| Case series | Easy quantitation of incidence | No control group, so cannot be used for hypothesis testing |
| Case reports | Cheap and easy method for generating hypotheses | Cannot be used for hypothesis testing |

Other: Pragmatic Trials; Registries; Self-Control; Meta-Analyses

Strom, PE Textbook

## Evidence Hierarchy




Evidence-Grade Hierarchy: US Preventive Services Task Force

## *"The optimal research method will be determined by the type of question"*

Does it work | Patient Perspective | Implementation/Cost

| | Effectiveness | Appropriateness | Feasibility |
|---|---|---|---|
| Excellent | • Systematic review<br>• Multi-centre studies | • Systematic review<br>• Multi-centre studies | • Systematic review<br>• Multi-centre studies |
| Good | • RCT<br>• Observational studies | • RCT<br>• Observational studies<br>• Interpretive studies | • RCT<br>• Observational studies<br>• Interpretive studies |
| Fair | • Uncontrolled trials with dramatic results<br>• Before and after studies<br>• Non-randomized controlled trials | • Descriptive studies<br>• Focus groups | • Descriptive studies<br>• Action research<br>• Before and after studies<br>• Focus groups |
| Poor | • Descriptive studies<br>• Case studies<br>• Expert opinion<br>• Studies of poor methodological quality | • Expert opinion<br>• Case studies<br>• Studies of poor methodological quality | • Expert opinion<br>• Case studies<br>• Studies of poor methodological quality |

Hierarchy of evidence: ranking of research evidence evaluating health care interventions.

Journal of Clinical Nursing 2003; 12: 77–84

## Observational Studies Advantages

**Advantages:**

Fewer restrictions on numbers (n) – generalizability.

Can more accurately assess rare adverse events.

Numerous outcomes can be studied.

Suited for long-term follow-up.

Fewer ethical restrictions.

Complex clinical situations where RCT are precluded.

Usually less expensive and faster.

## Observational Studies Disadvantages

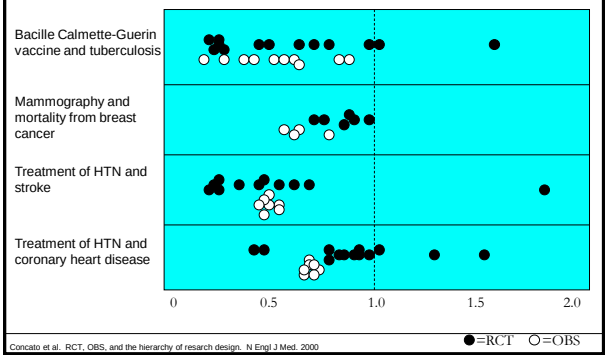
**Disadvantages:**

No randomization.

Usually data collected for alternative purpose and all relevant information may not be available (e.g., claims data).

Potential for confounding variables.

## Observational Studies vs. RCT




Concato et al. RCT, OBS, and the hierarchy of resarch design. N Engl J Med. 2000

## Estrogen and Cardiovascular Disease: Observational vs. RCT

*"Recent clinical trials demonstrating that hormone replacement therapy (HRT) does not prevent coronary heart disease in women have again raised doubts concerning observational studies."*

*Possible Explanations:*

Healthy User Effect

Women in the observational studies initiated ET or HT at or near the menopausal transition, at which point there is little or no arterial injury, whereas, in the WHI studies, older women, averaging approximately 12 years postmenopausal.

New User Design vs. Prevalent User Design

Acad. Sci. 1052: 43–56 (2005). Is the Estrogen Controversy Over? Deconstructing the Women's Health Initiative Study: A Critical Evaluation of the Evidence ; Kronos Early Estrogen Prevention Study (KEEPS); Am J Epidemiol 2003;158:915–920

## Case Report

*Case Reports: are reports of events observed in a single patient"*

***Spontaneous reporting:***
This is the reporting by healthcare professionals (and in some countries, patients, relatives and others) "spontaneously" of their suspicion of an adverse reaction having occurred. The reporting might be directly to the company marketing the product, or it could be made to the regulatory authority.


Panel 2: Criteria for judgment of causal associations[17,18,19]

**Temporal sequence**
Did exposure precede outcome?

**Strength of association**
How strong is the effect, measured as relative risk or odds ratio?

**Consistency of association**
Has effect been seen by others?

**Biological gradient (dose-response relation)**
Does increased exposure result in more of the outcome?

**Specificity of association**
Does exposure lead only to outcome?

**Biological plausibility**
Does the association make sense?

**Coherence with existing knowledge**
Is the association consistent with available evidence?

**Experimental evidence**
Have a randomised controlled trial been done?

**Analogy**
Is the association similar to others?

*FDA AERS Database & WHO* Vigibase

*Lancet 2002; 359: 248–52*

## Spontaneous Reporting

Strengths
- Passive surveillance
- Large sample size – potential to detect rare events.
- Cost
- Hypothesis generating
- Assumption of causality

Limitations
- Uncertainty that the suspect drug caused the event.
- Underreporting (numerator)
- Reporting bias
- No patient exposure data (denominator)
- No control group
- Latency of drug effect
- Inadequacy/incompleteness of reported information.

12

## Spontaneous Report Statistics

- The (proportional reporting ratio) PRR is a measure of the disproportionality of reports for a particular event for a drug of interest versus all other drugs in a database and is calculated as follows:
- PRR = $\frac{a / (a + c)}{b / (b + d)}$
- Where *a*, *b*, *c*, and *d* are defined as below.

| | Drug of interest | All other drugs in database |
|---|---|---|
| **Event(s) of interest** | ***a*** | ***b*** |
| **All other events** | ***c*** | ***d*** |

- PRR values based on cases for each Drug Event Combination (DEC).

13

## Factors Affecting Spontaneous Reports

Volume of drug use (more use → more reports)

Duration on the market (newer drugs → higher reporting rate- Weber Effect!)

Severity of event (greater severity → higher reporting rate)

Label status (unlabeled events → higher reporting rate)

Current trends (recent years → higher reporting rate)

Publicity → higher reporting rate

14

## Case Series

Case Series: collection of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described

Example: Active Surveillance – PEM study in the UK

Objective: To identify the events recorded following the use of newly marketed drugs selected for monitoring by the DSRU. These event data are assembled from large cohorts of patients and are used to identify suspected adverse drug reactions.

- Non-interventional study, Hypothesis generating technique
- Conducted by DSRU (independent registered charity )
- 'Real world' use of the new drug

## Registries

An organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention or disease state.

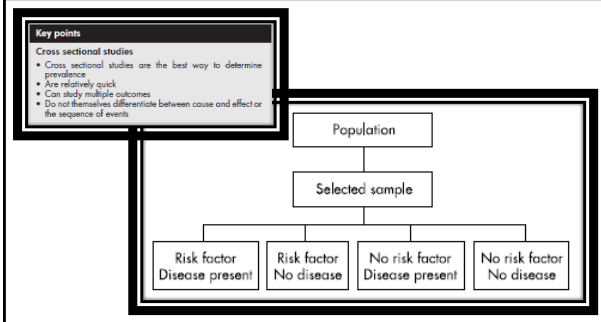
Goals:

- Determining clinical effectiveness, comparative effectiveness of a test or treatment
- Measuring or monitoring safety and harm of specific products and treatments, including comparative evaluation of safety.
- Measuring or improving quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.
- Assessing natural history, including estimating the magnitude of a problem; determining the underlying incidence or prevalence rate; examining trends of disease over time. For example Hypothesis generation studies

## Registries

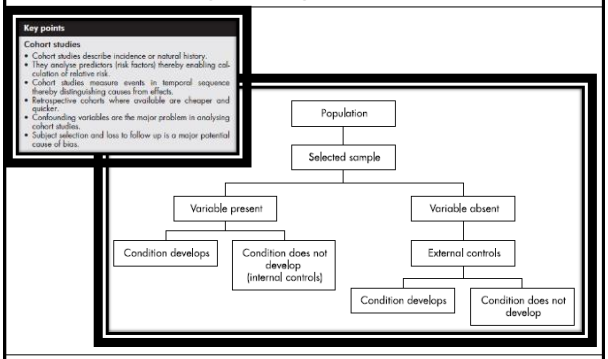
| Brand (Generic)<br>Basis for Risk Management Plan | Objective of Risk Management Plan | Prescriber Registry | Patient Registry | Pharmacy Registry |
|---|---|---|---|---|
| Accutane (Isotretinoin)<br>Teratogenicity | No fetal exposure | X | X | X |
| Clozaril (Clozapine)<br>Agranulocytosis | No agranulocytosis | X | X | X |
| Humatrope (somatropin [rDNA origin])<br>Limit Distribution | Limit distribution | X | X | |
| Tracleer (Bosentan)<br>Potential for serious liver injury and potential damage to a fetus | No serious liver injury; no fetal exposure | X | X | |

## Cross Sectional Study Design



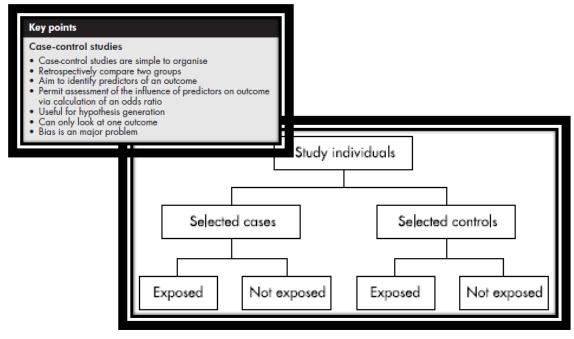

Emerg Med J 2003;20:54–60

## Cohort Study Design




Emerg Med J 2003;20:54–60

## Case Control Study Designs




Emerg Med J 2003;20:54–60

## Self Control Case Series

The self-controlled case series method was developed to investigate associations between acute outcomes and transient exposures, using only data on cases, that is, on individuals who have experienced the outcome of interest. Inference

Where incidence rates of events in exposed time periods are compared to incidence rates in unexposed time periods. Each case acts as its own control, thereby controlling for both measured and unmeasured confounding variables that do not vary over time.

Statist. Med. 2006; 25:1768–1797

## Self Control Case Series

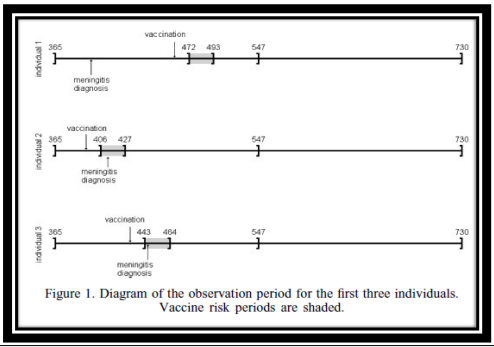



Figure 1. Diagram of the observation period for the first three individuals. Vaccine risk periods are shaded.

Statist. Med. 2006; 25:1768–1797

## RCT vs. Pragmatic Trials

RCT = Internal Validity

Pragmatic Trial = External Validity

Table 1 | **Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen**

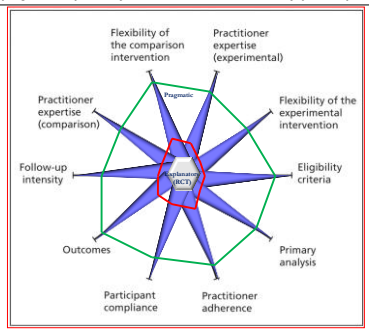
| | | |
|---|---|---|
| Question | Efficacy—can the intervention work? | Effectiveness—does the intervention work when used in normal practice? |
| Setting | Well resourced, "ideal" setting | Normal practice |
| Participants | Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded | Little or no selection beyond the clinical indication of interest |
| Intervention | Strictly enforced and adherence is monitored closely | Applied flexibly as it would be in normal practice |
| Outcomes | Often short term surrogates or process measures | Directly relevant to participants, funders, communities, and healthcare practitioners |
| Relevance to practice | Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented | Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented |

*BMJ 2008;337:a2390*

## How to distinguish pragmatic and explanatory trials

**The pragmatic-explanatory continuum indicator summary (PRECIS) tool**

- The pragmatic-explanatory distinction is continuous rather than dichotomous
- Typical pragmatic trials will likely land between narrow explanatory (RCT) and broad routine care (observational)
- The PRECIS tool can help assess the level of "pragmatism" when used as a discussion tool (e.g., in consultation with the EXPERT group)




Adapted from Thorpe et al. CMAJ 2009;180(10):E47-E57

## CONCLUSION

**The Unknown**

As we know,
There are known knowns (e.g., known safety concerns).
There are things we know we know.
We also know
There are known unknowns (e.g., suspected unmeasured safety concern).
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know (e.g., non-suspected unmeasured safety concerns).

*D.H. Rumsfeld —Feb. 12, 2002, Department of Defense news briefing*

## Sample Size Considerations for Pharmacoepidemiology Studies



## Pharmacoepidemiology

Exposure

- In pharmacoepidemiology studies the primary exposure of interest is of a drug.

Outcomes

- Outcomes potentially related to drug exposure

## Why calculate sample size?

Need a sufficiently large sample size to detect a statistically significant finding.

Sample size calculations are an approximation

- Use available data for assumptions (literature, pilot study)
- Always better to have a larger than needed sample than not enough
- Can be an iterative process

# Cohort Studies



## Cohort Studies

Definition

- Studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome

## Cohort Studies

To calculate sample size you must a priori specify:

- Type I(α) error considered tolerable, and whether it's one-tailed or two-tailed
- Type II(β) error considered tolerable
- Minimum *relative risk* to be detected
- Expected incidence of the disease in the unexposed control group
- Ratio of unexposed controls to exposed study subjects

## Cohort Studies

Type I error (α) considered tolerable,

- The more tolerant you are of type I error (α) the smaller the sample size needed.
- Type I error (α) is typically set at .05

Specify α as one-tailed or two-tailed

- Set based on the directionality of the outcome
  - If probability could be greater o less than 0 = two tailed
  - If probability can only be greater than OR less than 0 = one tailed

## Cohort Studies

Type II (β) error considered tolerable

- The more tolerant of Type II error the smaller the sample size required
- β is typically set at 0.1 or 0.2

Power (1- β)

- The probability of detecting a difference when one truly exists
- If β= 0.1, then (90%power)
- If β= 0.2, then (80%power)

## Cohort Studies

Minimum relative risk to be detected

- Minimum effect size to be detected (RR)
- Smaller RR requires larger sample size
- Important to note that if a relative risk of 2.5 is selected then a relative risk of 2.2 may not be detected as a significant finding.

## Cohort Studies

- Expected incidence of the disease in the unexposed control group
- A rare outcome will require a larger sample size

## Cohort Studies

- Ratio of unexposed controls to exposed study subjects
- A study has the most statistical power for a given number of study subjects if it has the same number of controls as exposed subjects
- If the number of exposed are limited then power can be increased by increasing the number of unexposed controls.

## Cohort Studies

Formula to calculate sample size (one tailed)

$$N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{pR(1-Rp)+\frac{p(1-p)}{K}}\right]^2$$

Where $U = \frac{K_p + pR}{K+1}$

| | |
|---|---|
| *p*= incidence of disease in controls | Z= unit normal deviates corresponding to α and β |
| *R*= minimum RR to be detected | K= ratio of controls to exposed |

If two tailed substitute $Z_{1-\alpha/2}$ for $Z_{1-\alpha}$

## Cohort Studies

Examples

- Class exercise

# CASE-CONTROL STUDIES

## Case-Control

- Must a priori specify:
  - Type I(α) error considered tolerable, and whether it's one-tailed or two-tailed
  - Type II(β) error considered tolerable
  - Minimum *odds ratio* to be detected
  - Expected p*revalence* of the exposure in the control group
  - Ratio of controls to diseased study subjects

## Case-Control

- Expected *prevalence* of the exposure in the control group
- Ratio of controls to diseased study subjects
  - Generally no more than 3:1 or 4:1

## Case-Control

Formula to calculate sample size (one tailed)

$$N = \frac{1}{[p(1-V)]^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{\frac{p(1-p)}{K+V(1-V)}}\right]^2$$

Where $V = \frac{pR}{1+p(R-1)}$

| | |
|---|---|
| *p*= incidence of disease in controls | Z= unit normal deviates corresponding to α and β |
| *R*= minimum RR to be detected | K= ratio of controls to exposed |

If two tailed substitute $Z_{1-\alpha/2}$ for $Z_{1-\alpha}$

## Case-Control Studies

Examples

- Class exercise

## Case Series

Useful in calculating the incidence of a condition among users of a newly marketed drug.

Used to determine whether a disease occurs more frequently than some predetermined incidence in exposed patients.

- Most often used in cases where predetermined incidence is zero, or occurrence is rare

# Meta-analysis in Pharmacoepidemiology

45

## Meta-analysis

Definition

- The statistical analysis of a collection of analytic results for the purpose of integrating the findings.
  - State of the art literature review.

Used to identify sources of variation among study findings and, when appropriate, to provide an overall measure of effect as a summary to those findings

Limitations

- Biases in the component studies and the great diversity in study designs and populations

Contributions

- Efficient and intelligent use of existing data prior to (or instead of) embarking on a large, primary data collection effort

## Meta-analysis

Combination of statistical methods and thorough and systematic qualitative review

Systematic, structured, objective presentation and analysis of available data

Example

- Summary of a group of randomized clinical trials for a particular therapy of a particular outcome. Presents the overall measure of efficacy of treatment
- Common non-experimental use tends to focus on exploration on reasons for disagreement among the results of prior studies, including the possibility of bias.

## Meta-analysis

Utility

- Study of uncommon adverse outcomes of therapies free of confounding and bias of non-experimental studies
- Exploration of reasons for inconsistencies of results across previous studies
- Exploration of subgroups of patients in whom therapy might be more or less effective
- Combination of studies involved in the approval process for new therapies

## Meta-analysis

Methodological problems

- Quality of original studies
- Combinability of studies
- Publication bias
- Bias in the abstraction of data

## Meta-analysis Methodological Problems

Quality of original studies

- Meta-analysis only as good as the studies selected

Combinability of Studies

- To be determined on an individual basis with a well supported justification

## Meta-Analysis Methodological Problems

Publication bias

- Statistically significant results are published more easily than nonsignificant results

Bias in the abstraction of data

- A type of retrospective analysis and takes on retrospective analysis potential bias
- Selection and rejection of studies

## Meta-analysis Methodological Problems

Combinability of results of diverse studies

- If less stringent inclusion criteria and the studies are too heterogeneous then possibility that the average finding may not apply o any particular subgroup of patients
  - Although diversity of designs may allow for understanding the factors that modify the effectiveness (or toxicity) of a drug

## Meta-analysis
## Methodological Problems

Publication Bias

- Published data may represent a biased subset of all studies that have been done.
- It is more likely that studies with statistically significant findings will be published than studies with no significant findings.
- To address
  - Funnel plot
    - Plotting of the effect size (e.g. the risk difference) against a measure of study size or the inverse of the variance of the individual effect sizes.
    - An asymmetry of bite-out of the funnel shape will indicate possible existence of publication bias
  - Other

## Meta-analysis
## Methodological problems

Solutions

- Define the purpose
- Perform literature search
- Establish inclusion/exclusion criteria
- Collect the data
- Perform statistical analysis
- Conclusions and Recommendations

Vita, A; De Peri, L; Sacchetti, E. Antipsychotics, Antidepressants, Anticonvulsants, and Placebo on the Symptom Dimensions of Borderline Personality Disorder: A Meta-Analysis of Randomized Controlled and Open-Label Trials. *Journal of Clinical Psychopharmacology*: October 2011 - Vol 31 (5 ): 613-624.

The aim of this study was to quantitatively review randomized controlled trials (RCTs) and open-label trials analyzing the efficacy of antidepressants, mood stabilizers, and antipsychotics for the treatment of the core symptoms of borderline personality disorder (BPD). Using a similar meta-analytic approach, the efficacy of placebo on the same core symptoms of BPD was evaluated. The risk of discontinuation of each of the medication classes reported in the studies was also analyzed to establish the major causes of discontinuation. MEDLINE (1966 to June 2010) and EMBASE (1980 to June 2010) databases were systematically searched to identify relevant RCTs and open studies. The primary outcome was improvement in the specific core symptoms of the disorder: affective dysregulation, impulsive-behavioral dyscontrol, and cognitive-perceptual symptoms. Evidence from RCTs and open studies suggests that drug treatment, especially with mood stabilizers and antipsychotics, may be effective for treating affective dysregulation and impulsive-behavioral dyscontrol. Antipsychotics were also effective in reducing cognitive-perceptual symptoms. Antidepressants failed to show efficacy in treating BPD symptom dimensions other than affective dysregulation. Our analyses of the placebo arm of RCTs showed a significant improvement of symptomatology in these patients also. There were no significant differences in overall dropout rates between patients on medications and those on placebo. In conclusion, the efficacy of pharmacological treatment on the symptom dimensions of BPD has been shown by various independent meta-analyses, with a positive effect of drug treatment on the core symptoms of BPD and some documentable differences in terms of efficacy between different drug classes in each of the symptom domains.

# Thank you!