



# Introduction to Pharmacoepidemiology

Overview  
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# Topics

- Definitions
  - Pharmacoepidemiology
  - Pharmacovigilance
- Overview of Epidemiologic Principles
- Application of Epidemiologic Principles in Drug Monitoring
  - Signal Detection
  - Pharmacovigilance Plan
    - Safety Specification
    - PV Plan
- Technical Solutions for Pharmacoepidemiology
  - AERS
  - Q-scan
- Exercise
- References

# Definition

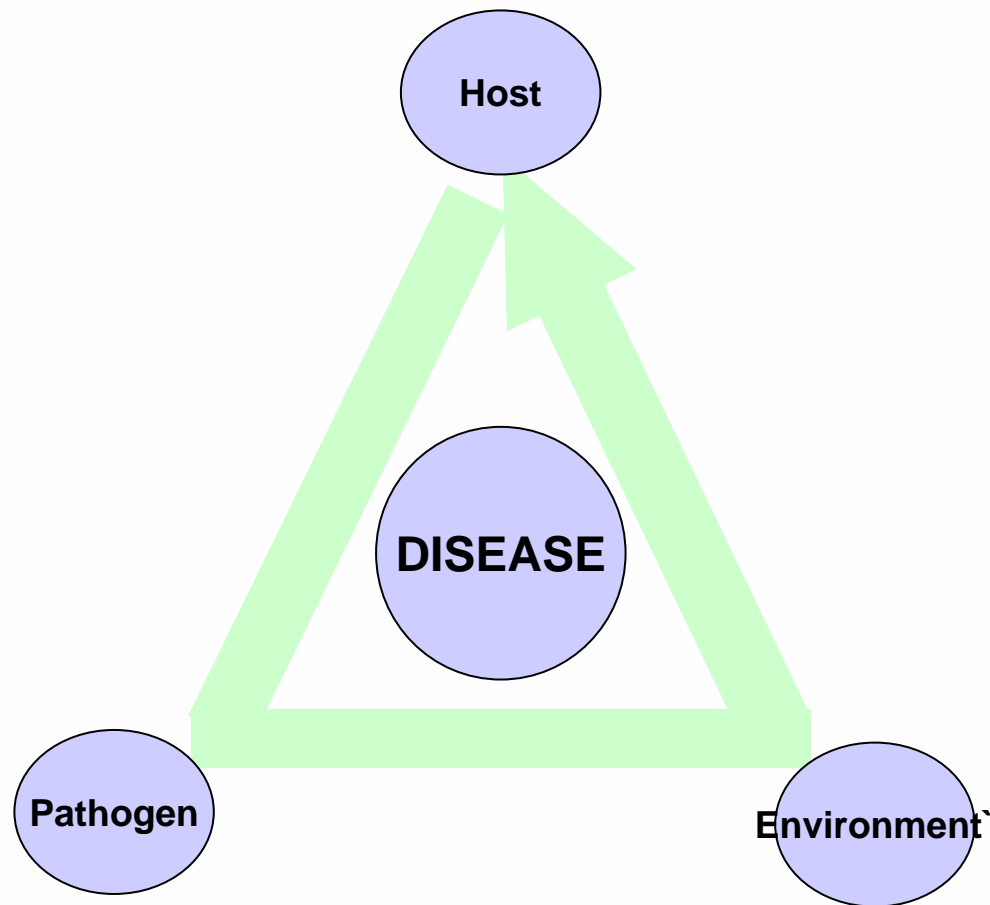
- *Pharmacovigilance* – Two pervasive definitions (Abenhaim, Moore, & Begaud, 1999)
  - Watchfulness in guarding against danger from products or providing for safety of the product
    - Expansive beyond just regulations and frames the construct for use in academia and the sciences
  - The collection and scientific evaluation of adverse drug reactions (ADR), under normal conditions of use for regulatory purpose.
    - Restricts the concept to regulatory compliance only
- *Pharmacoepidemiology* – The application of epidemiologic techniques used to study the effects of drugs in populations
  - First mentioned in the early 1980's (Abenhaim, Moore, & Begaud, 1999)

# Epidemiology Overview

- The study of determinants of health and illness in populations serving as the science behind public health and preventative medicine
  - Concerned with relationships between disease and exposures
    - While these correlations do provide insight into causal plausibility, correlation between disease and exposure does NOT constitute causation

# Epidemiology Methods

- Epidemiology Triangle



# Epidemiology Methods

- Epidemiology Methods are segregated into two broad categories
  - Experimental
    - Study designs used to describe (report) the distribution of exposure and effect
  - Observational
    - Study designs used to analyze and understand the degree of association between exposure and effect

# Epidemiology Measures

## Occurrence

### Incidence

1. Incidence Proportions
2. Incidence Rates
3. Cumulative Incidence

### Prevalence:

1. Lifetime Prevalence
2. Point Prevalence
3. Period Prevalence

## Association

### Relative (calculated by division)

1. Risk Ratio  
or Relative Risk  
or Rate Ratio (RR)
2. Odds Ratio (OR)

### Absolute (calculated by subtraction)

1. Attributable Risk
2. Rate Differences

# Pharmacoepidemiology Overview

- Application of epidemiologic principles described above to the bio-pharmaceutical industry
  - Starts with Signal Detection
  - Results in Creation of Pharmacovigilance Plan (or PV Risk Management Plan)
    - Safety Specification
    - PV Plan (PVP)

# Signal Detection

- When determining if a particular safety issue warrants inclusion in a PVP, a company must weigh its risk to benefit ratio for further research of an issue
  - The use of signal detection methods aids in the process of clarifying the presence of a true signal
- The term *signal* in PV is often used as a synonym to *signal of disproportionate reporting* (SDR)
  - Technically, a true *signal* includes a more thorough evaluation (including clinical plausibility, pharmacologic method of action etc.) compared to the simple statistical measurement used to identify an SDR

# Measures of Signal Detection

- All measures calculated from a 2X2 Table
  - Proportional Rate Ratio (PRR)
  - Reporting Odds Ratio (ROR)
  - Relative Reporting Ratio (RRR)
  - Information Component (IC; Bayesian)

	<b>Event (R)</b>	<b>All Other Events</b>	<b>TOTAL</b>
<b>Medicinal Product (P)</b>	A	B	<b>A+B</b>
<b>All other medicinal products</b>	C	D	<b>C+D</b>
<b>TOTAL</b>	<b>A+C</b>	<b>B+D</b>	<b>N=A+B+C+D</b>

# Signal Detection

- All measures of SDR are basically calculations of OBSERVED/EXPECTED event/drug reports
  - Since the EXPECTED data is actually originating from the same pool as the OBSERVED data, we CANNOT use a PRR as an RR nor a ROR as an OR
  - EXPECTED data in epidemiology comes from sources other than the OBSERVED
- In PV, the EXPECTED data is also referred to as the “background”
- What you include in the “background” is a point of contention in the industry and no real rules are present (Gogolak, 2003)

# Signal Detection

- Since the simple calculation is  $O/E$ , the relationship between background and the statistic of interest is inversely related:
  - As the background increases the resulting statistic decreases
    - Large E results in small PRR
  - As the background decreases the resulting statistic increases
    - Small E results in large PRR

# PV Planning and Documentation

- Whatever statistic used, they are wrought with assumptions and limitations that must be clearly addressed before expending company time and money on further evaluation
- The EMEA has established a guidance document interpreting the ICH guidance E2E on the documentation of a PV Plan (European Medicines Agency (EMA), 2006a)
  - The PV Plan can be seen as your company's tool justifying and focusing your PV activities

# Safety Specification

- This section of (or individual document) is intended to summarize the existing knowledge and limitations of that knowledge concerning the product
- Included Elements *should* include
  - Non-Clinical Drug information
    - Toxicity
    - Drug interactions
    - General Pharmacology
  - Clinical
    - Limitations of Human Safety Data
    - Populations not studied in the pre-approval stage
    - Adverse Events/Adverse Drug Reactions
    - Potential Interactions
    - Epidemiology
    - Pharmacologic Class Effects

# Pharmacovigilance Plan

- PV Plan documentation
  - Designed to explain the company's approach to addressing the limitations and findings in the safety specifications documentation
- Should contain the following information
  - Summary of ongoing safety issues
  - Description of Routine PV Initiatives
  - Action plan for safety issues
  - Specific protocols may be added as references to this document
  - Summary of actions to be completed
- A PV Plan is a living document and is revised as needed based on regulatory submissions (such as PSUR and NDA Periodic) and the changing landscape of the safety data and knowledge

# Technical Solutions

- To aid in PV methods, safety systems are created like AERS
  - These systems store the data, prepare reports for submission and provide information for case and case series analysis

# Technical Solutions

- Data mining tools provide a tremendous assistance in the evaluation of a signal
  - Right now, several tools provide a method to data-mine the world-wide reporting of spontaneous event data with a out of the box user interface
    - FDA – AERS Database
    - WHO – Vigibase Database (~3.7 million reports)
  - Tools such as Q-Scan, Lincoln Technologies among others

# Technical Solutions

- Use of these databases requires that certain assumptions be made
  - Drugs used in the marketplace are used by a representative sample of the greater population
- Any information derived from these databases should be interpreted using the limitations of the data contained therein (Edwards, 1999)
  - Limited clinical quality of data
    - USA allows reporting into the AERS system from anyone (Health care provider {HCP} or not)
    - EMEA only allows reporting by HCP thus typically more complete clinical information

# Technical Solutions

- Underreporting of serious events
  - Changes the number of expected events
  - “Weber Effect”: The peak reporting for events in a drug on market occurs within the first 2 years of approval (Hartnell, & Wilson, 2004) during the initial 5 year marketing period
- Over reporting of events of non-interest (expected non-serious)
- False Causality attribution
  - Signals *ARE NOT CAUSAL INDICATIONS*
  - They are disproportionate reporting indicators

# Summary

- PV is a fascinating relatively new field of product development
- Signals are detected using ratios of Observed number of event/drug occurrences divided by some Expected count (O/E)
  - ROR
  - RR
  - PRR
  - IC
- Signals are not estimates of incidence, prevalence nor are they descriptors of causality
- Caution should ALWAYS be exercised when evaluating data originating from spontaneous reports
- The ICH PV Plan helps organizations focus their information and aids in only spending money on true events of interest

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# Contact Information

Rodney has over 12 years experience in clinical research including raw laboratory experimentation, clinical data management, clinical trial design, dictionary coding and pharmacovigilance.

Rodney has worked for BioPharm Systems for nine years now serving in a variety of roles all related to the technical and/or clinical implementations of software systems used in the clinical trial process.

Prior to coming to BioPharm Systems Rodney worked at pharmaceutical and technology companies in the Dictionary Coding, Statistical Programming and Data Management areas.

In addition to his current work at BioPharm Systems, Rodney holds an Associate faculty position at Walden University teaching a variety of classes in their Masters of Clinical Research program.

Rodney holds a Bachelor of Science in Genetic Engineering, a Masters of Public Health in International Epidemiology and a Ph.D. in Epidemiology focusing on Social Epidemiology



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