Incorporating Clinical Information into the Label

Labels without Categories: A Workshop on FDA's Pregnancy and Lactation Labeling Rule
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PLLR Draft Guidance Reference

- *4.Data, a.Human Data (pg 11-12)*: describe the data that provide the scientific basis for the information presented in the Risk Summary and Clinical Considerations
  - Include Positive & Negative findings (no heading if absent human data)
  - Update label as new data become available
  - Evaluate quality & quantity of data for inclusion in label
  - Describe adverse outcomes/rxns/effects, including:
    - Data source (RCT, Registry, Study type etc)
  - Number of subjects & study duration
  - Exposure timing, duration, and dose
  - Data limitations including biases & potential confounders
  - Include comparison group data, data CIs, & power calculations

Presentation Outline

- Overview of study designs, basic applied statistics, quality & how to interpret results
- Overview of where clinical data sources are found
- Summarizing data information for the label
- Discussion of whether sufficient clinical information exists to include in the label: What is the threshold for inclusion? Is it of sufficient quality and/or robust enough? When are there enough human data to make the label?

Hierarchy of Evidence

- Systematic reviews and meta-analyses
- **RCT**s with definitive results (CIs that do not overlap clinically significant threshold effect)
- **RCT**s with non-definitive results (point estimate suggests clinically significant effect but with overlapping CIs)
- **Cohort studies**
- **Case-control studies**
- Cross sectional surveys
- Case reports: rarely sufficient to characterize risk. Notable exception: thalidomide.

What about Registries?

- **Registries** come in several forms and they can parallel different study designs
- Basic idea: an observational study method. A form of surveillance, on the continuum from passive surveillance to active
  - Optimally, Registries are conducted with the rigor of a cohort study, including recruitment strategies, carefully selected comparison group(s), exposure/outcome ascertainment, & indiv. follow-up
- PERs the most common type of post-approval study in pregnant women required/request by FDA

What about Registries?

- Shortcoming: often fail to provide useful info for reasons including:
  - low enrollment, retrospective cases
  - Prevalence of disease in pregnant women
  - Awareness of PER, by HCPs & patients

⇒**Is shortcoming due to our expectations? Is study designed for signal generation or for hypothesis testing?**

⇒Registries can provide a valuable contribution to **body of evidence**

Observational studies vs RCTs

Observational studies - cohort design:

- Women ‘decide’ if they are going to use the exposure of interest and which type
- Variation in how much exposure & when exposure occurs

Clinical Trials:

- Women are randomized to exposure of interest/type
- Very few RCTs

=> We will focus on observational studies…

Study Design Overview

Cohort study

- To determine causes of disease

Population free from disease → Sample followed → Incident cases of new disease

Case-control study

Patients with disease, or with pre-specified outcome, and comparison group without disease → ***Look back to determine exposure to possible risk factors or causes***

Cross-sectional study

Patients with characteristic of interest → Look at same time to examine other characteristics

Cohort Study - Basic Design

Exposed

Disease?

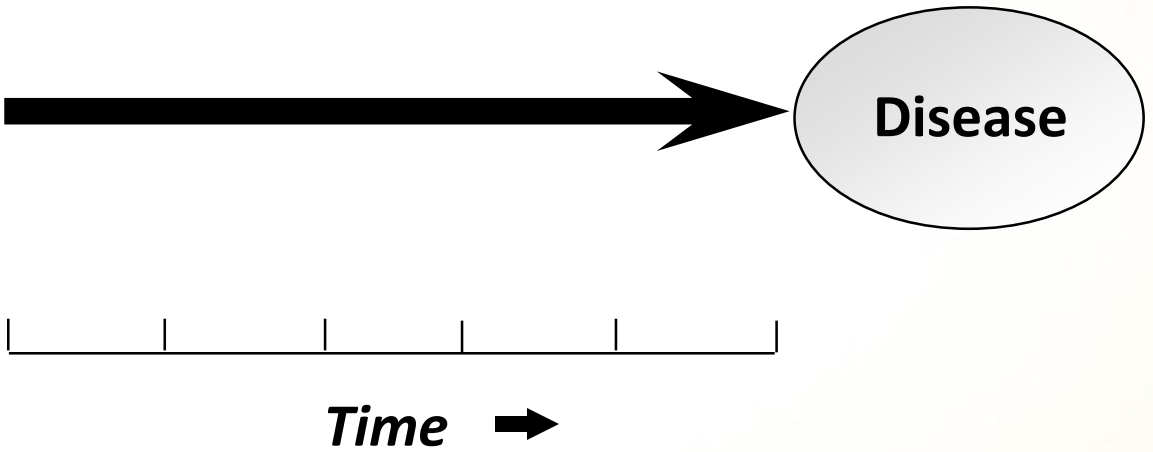
Unexposed

Disease?

Time ➡

Cohort Study: Single Population Design

Healthy population with exposure assessed



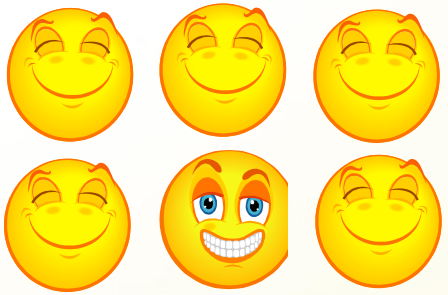
Case-Control Study - Basic Design

Diseased

Exposed/
Unexposed

Non-diseased

Exposed/
Unexposed



Time

Prospective vs. Retrospective Cohort

Prospective

Retrospective/Historical

Time

Disease

Cohort Studies - Advantages

- Can select for rare exposures
- Multiple effects/outcomes from a single exposure
- Clarity of temporal sequence (ie. establish timing and directionality of events)
- Ability to directly calculate incidence rates in both the exposed & unexposed groups
- Ethically safer relative to RCT
- Subjects can be matched
- Eligibility criteria & outcome assessments can be standardized
- Administratively easier & cheaper than RCT.

Cohort Studies - Disadvantages

- Comparisons may be difficult to identify
- Exposure may be linked to a hidden confounder
- Blinding, if needed, is difficult
- Randomization not present
- For rare disease, need large sample sizes
- May need long follow-up (e.g. DES)
- Problems resulting from loss to follow-up (bias)
- Cost & time related to sample sizes required, methods of assessing exposure & disease

Case-Control Studies - Advantages

- Quick and cheaper than a cohort
- Only feasible method for very rare disorders or those with long lag between exposure & outcome;
- Fewer subjects needed.

Case-Control Studies - Disadvantages

- Reliance on recall or records to determine exposure status
- Potential confounders
- Selection of control groups is challenging
- Potential bias: recall, selection

Cohort Study - Quantifiables

- Incidence (occurrence) rates in expos. & unexposed
- Relative risk (RR) or Odds Ratio (OR)

RR ≡ relative difference in risk associated with expos.

$$RR = \frac{R_1}{R_0}$$

Risk Difference (RD) = absolute difference in risk associated with an exposure

$$RD = R_1 - R_0$$

R_1 ≡ risk in exposed group, R_0 ≡ risk in non-exposed

Case-Control Study - Quantifiables

Can we compute incidence rates in exposed & unexposed? NO – why?

- Odds Ratio (**OR**)

	NTD+	NTD−
Folic Acid+	10	10,703
Folic Acid−	39	11,905

$$OR = \frac{A_1 B_0}{B_1 A_0} = \frac{10 \cdot 11{,}905}{10{,}703 \cdot 39} = 0.29$$

If OR = 3.0, the odds of an exposed person developing outcome are 3X that of an unexposed person

If OR = 0.3, the odds of an exposed person developing outcome are ~ one third that of an unexposed person

Interpretation of Point Estimate (OR or RR)

Use OR as example:

- Relative odds associated with exposure
  OR = 1 $\Rightarrow$ no association (expos. to adverse outcome)
  OR > 1 $\Rightarrow$ positive association
  OR < 1 $\Rightarrow$ negative/protective association

- Size of OR indicates strength of association

- OR ≈ RR when disease rare (i.e., risk < 5%); when disease not rare, OR still a valid measure of association

“To error is human”

- Science emphasizes systematic, repeatable, carefully-conducted observation
- Laboratory investigations are highly controlled, to minimize unwanted influences
- Human sciences must contend with many threats to validity….the good news is that we’re not lab rats
- Importance of human data: animal model findings don’t always predict findings in humans and v.v.

“To error is human”

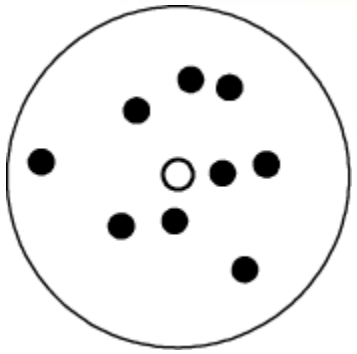
Any epidemiologic study presents many opportunities for error in relation to:

- Selection of study participants
- Classification and measurement
- Comparisons and interpretation

- These systematic error sources are in addition to sampling variability (random error)

Random Error (Imprecision)

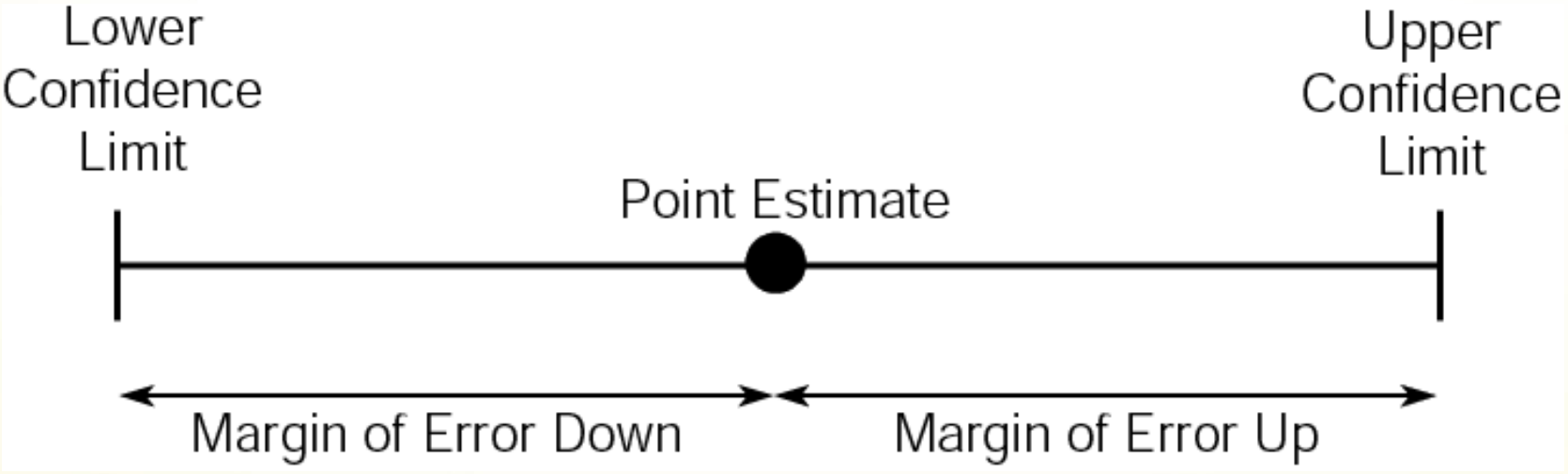
- Random error
  = imprecision
  = balanced scatter
- Dealt with via probability models (e.g., Normal distributions)
- Methods:
  - Confidence intervals
  - Hypothesis tests



Confidence Intervals

- **Confidence Interval (CI):** surrounds point estimate with **margin of error** $\Rightarrow$ **CI locates** the parameter with specified level of confidence (e.g., 95%)

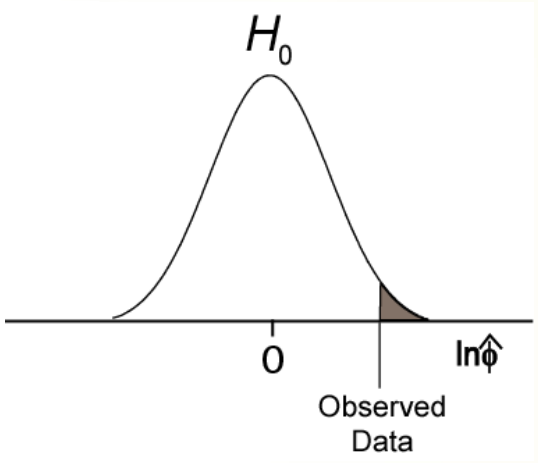
- The width of the CI quantifies the **precision** of the estimate (narrow CI $\rightarrow$ precise estimate)



P-values in a Nutshell

P value tells us the probability of an event occurring due to chance alone

- Null hypothesis
  H_0: RR = 1 (no effect)
- *Small P*-value $\Rightarrow$ *strong* **evidence *against* H_0**



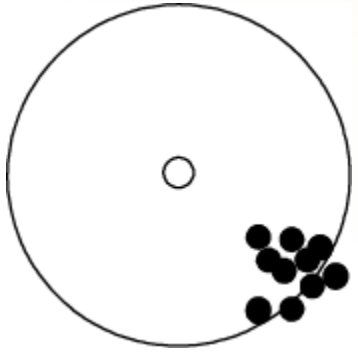
- *P* = .05 is a guide, not a cutoff
- Rough guide:
  P ≤ .10 $\Rightarrow$ marginally significant evidence against H_0
- P ≤ .01 $\Rightarrow$ very significant evidence

Systematic Error (Bias)

- ***Bias*** = systematic error in inference (*not* an imputation of prejudice)
- **Direction** of bias

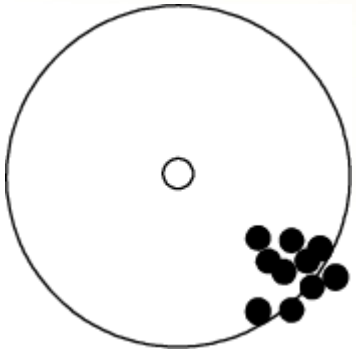
  Toward the null (*RR* underestimates true effect)

  Away from null (*RR* overestimates true effect)



Categories of Bias

- **Selection bias** –study participants selected in a way that favors a certain outcome
- **Information bias** – misinformation favoring a particular outcome
- **Confounding** – extraneous factors cause bias



Confounding

"Mixing of effects"

- Some other risk factor may be responsible for at least some of the association under investigation.

Common Confounders:

- Age -- e.g., exposed persons are older
- Sex -- e.g., more exposure in men
- Risk factors - more exposed persons (or unexposed) smoke(-), exercise(+), eat vegetables(+), use recreational drugs(-), . . .

Control of confounding

Controlling confounding means doing something to make comparison more fair:

- Exclude people who have the risk factor ("restriction")
- Stratified analysis (adjustment, standardization)
- Mathematical modeling (e.g., regression)

Control of unknown confounders: e.g. randomize

Effect Modification / Interaction

- The magnitude or direction of an association varies according to levels of a third factor

- Unlike confounding, effect measure modification should be described and reported, rather than controlled.

General Quality Evaluation of Studies

- Choice of population & comparisons…potential for bias
- Understanding underlying prevalence of exposure & preval. of outcome …belongs in the 8.1 Risk Summary
- Define & measure exposure (medication dose, timing not observed) & outcome (e.g. dysmorphology exam)
- Some maternal disease & some meds: episodic
- Identifying start & end of pregnancy…expos. windows
- Maternal disease (‘confounding by indication’)
- Early outcomes (fertility, early pregnancy loss)…difficult to pick up
- Availability of important covariate information

Suggested Clinical Data Resources

- Publications:
  Include studies from classical study populations, long standing case-control studies (Slone, Metropolitan Atlanta Birth Defects), study populations formed using large linked automated databases

- Registries:
  FDA Office of Women's Health Research online http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm > click "Find A Registry" for listing VAMPSS

- Manufacturer data, early phase studies
- Abstracts/unpublished data?

- www.clinicaltrials.gov

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How Much Data to Include?

- What is the threshold for inclusion?
- Is it of sufficient quality and/or robust enough?
- When are there enough human data to make the label?
  - No straightforward answers, but you now know the basics of evaluating hierarchy & quality of studies
  - Requires expertise & informed judgement

Questions?

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